COST-EFFECTIVENESS ANALYSIS OF A PROSPECTIVE BREAST CANCER SCREENING PROGRAM IN TURKEY

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Approval of the Graduate School of Social Sciences

_____

Prof. Dr. Meliha Altunışık
Director

I certify that this thesis satisfies all the requirements as a thesis for the degree of Master of Science

_____

Prof. Dr. Erdal Özmen
Head of Department

This is to certify that we have read this thesis and that in our opinion it is fully adequate, in scope and quality, as a thesis for the degree of Master of Science.

_____ _____

Assoc. Prof. Dr. H. Hakan Yılmaz
Co-Supervisor

Assoc. Prof. Dr. Ebru Voyvoda
Supervisor

Examining Committee Members

Assoc. Prof. Dr. Ebru Voyvoda (METU, ECON)_____

Assoc. Prof. Dr. H. Hakan Yılmaz (AU, PF) _____

Assoc. Prof. Dr. Nuray Yazıhan (AU, MF) _____

Assoc. Prof. Dr. Şirin Saraçoğlu (METU, ECON)_____

Assoc. Prof. Dr. Murat Kırdar (METU, ECON)_____

I hereby declare that all information in this document has been obtained and presented in accordance with academic rules and ethical conduct. I also declare that, as required by these rules and conduct, I have fully cited and referenced all material and results that are not original to this work.

Name, Last name:

Signature :

ABSTRACT

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Astım, Engin
M.S., Department of Economics
Supervisor : Asst. Prof. Dr. Ebru Voyvoda
Co-Supervisor: Assoc. Prof. Dr. H. Hakan Yılmaz

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Cancer is the second leading cause of death among the world and it has an increasing share among all causes of death. Economical burden of cancer is increasing especially in high and middle-income countries. Leaving cancer in competitive markets would lead to inefficiencies; hence governments should intervene in the market and make public decisions in struggling cancer. Among all cancer types breast cancer has the highest incidence and mortality rates in females. Causes of breast cancer still remains indeterminate and only way to cope with breast cancer are by early diagnoses. Early diagnoses can best be achieved by regular mammography screenings. This study analyzes the possible outcomes of implementing regular breast cancer mammography screening program in Turkey. A simulation model is constructed and run for 10 years, to obtain the costs and benefits of such a screening program. Costs of such a program include the screening costs and costs due to abnormal mammograms. Benefits, on the other hand are reduced treatment costs due to early diagnosis, reduced mortality and morbidity. Simulation model is run for 11 different screening strategies for determining the optimal screening strategy in terms of screening interval and minimum age to screen. The necessary data is obtained from hospital records, Cancer Early Diagnosis and Treatment Center records, IMF, WHO and TUIK databases and literature. Results of the simulation suggest that women over 40 in Turkey should be screened biennially for economical efficiency.

Keywords: Breast cancer screening, mammography, cost-effectiveness

ÖZ

TÜRKİYE'DE UYGULANACAK OLASI BİR MEME KANSERİ TARAMA PROGRAMININ MALİYET-ETKİNLİK ANALİZİ

Astım, Engin
Yüksek Lisans., Ekonomi Bölümü
Tez Danışmanı : Yrd. Doç. Dr. Ebru Voyvoda
Yardımcı Danışman: Doç. Dr. Hakkı Hakan Yılmaz

Ocak 2010, 108 sayfa

Kanser dünyada ölüm nedenleri arasında ikinci önde gelen nedendir ve tüm ölüm nedenleri arasında giderek artan bir paya sahiptir. Kanserin ekonomik yükü özellikle yüksek ve orta gelirli ülkelerde giderek artmaktadır. Kanseri rekabetçi piyasalara bırakmak ekonomik verimsizliğe yol açabilir, dolayısıyla hükümetlerin kanser piyasasına müdahale etmeleri ve kanserle mücadele için kamu politikaları sunmaları gerekir. Tüm kanser türleri arasında meme kanseri kadınlarda en yüksek insidans ve mortalite oranlarına sahiptir. Meme kanserinin nedenleri bilinmemektedir ve meme kanseri ile başa çıkmanın tek yolu erken tanıdır. Erken tanı en iyi düzenli mamografi taramaları ile elde edilebilir. Bu çalışmada, Türkiye'de düzenli olarak mamografi tarama programı uygulanmasının olası sonuçları analiz edilmiştir. Bu bağlamda olası bir tarama programının fayda-maliyet analizini yapabilmek için bir simülasyon modeli inşa edilmiş ve 10 yıllık bir sure için çalıştırılmıştır. Maliyetler tarama masrafları ve anormal mamogram maliyetlerinden oluşur. Faydalar ise, azalan tedavi maliyetleri ile azalan mortalite ve morbiditeyi içerir. Simülasyon modeli tarama aralığı ve taranacak minimum yaşı belirlemek için 11 farklı tarama stratejisi için çalıştırılmıştır. Gerekli veriler hastane kayıtlarından, Kanser Erken Teşhis ve Tedavi Merkezleri kayıtlarından, IMF, DSÖ ve TÜİK veritabanları ve literatürden alınmıştır. Simülasyon sonuçları, Türkiye'de 40 yaşın üzerindeki kadınların iki yılda bir taranmasının ekonomik açıdan etkin sonuç olduğunu göstermektedir.

Anahtar kelimeler: Meme kanseri tarama programı, mamografi, maliyet-fayda

To My Wife

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1 INTRODUCTION

In medical terms cancer can basically be defined as an abnormal growth of cells which tend to reproduce in an uncontrolled way and, in some cases, to metastasize (spread) (http://en.wikipedia.org, 2010). In economical terms, on the other hand, it can be described as one of the biggest and to be tackled in first place economical troubles that causes huge amount of economical resources to be wasted, which include both medical care costs that spent in treatment and rehabilitation processes of those who have cancer, and the labor force loss.

According to statistical data collected by world health organization from the member countries, worlds leading causes for death are cardiovascular disease, infectious and parasitic disease and then malignant neoplasm, i.e. cancer, respectively. (Figure 1)

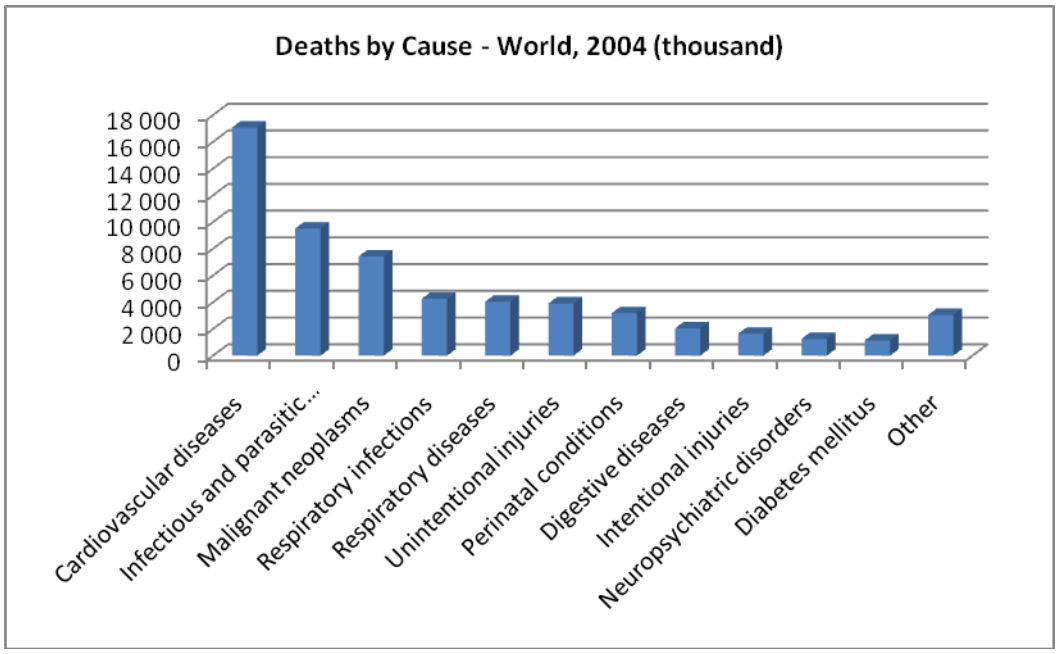

Figure 1: Deaths by Cause –World, 2004, WHO, 2004

The data suggest that there has been 7,424 thousand deaths occurred due to cancer by the year 2004. This corresponds to the fact that 13 of every 100 people died due to cancer in 2004.

Analyzing death reasons for Turkey brings out similar results. The Figure 2 illustrates that cancer is second leading cause of death for Turkey with 48.3 thousand deaths by the year 2002. (www.ketem.org, 2010) This corresponds to the 11% of all occasions.

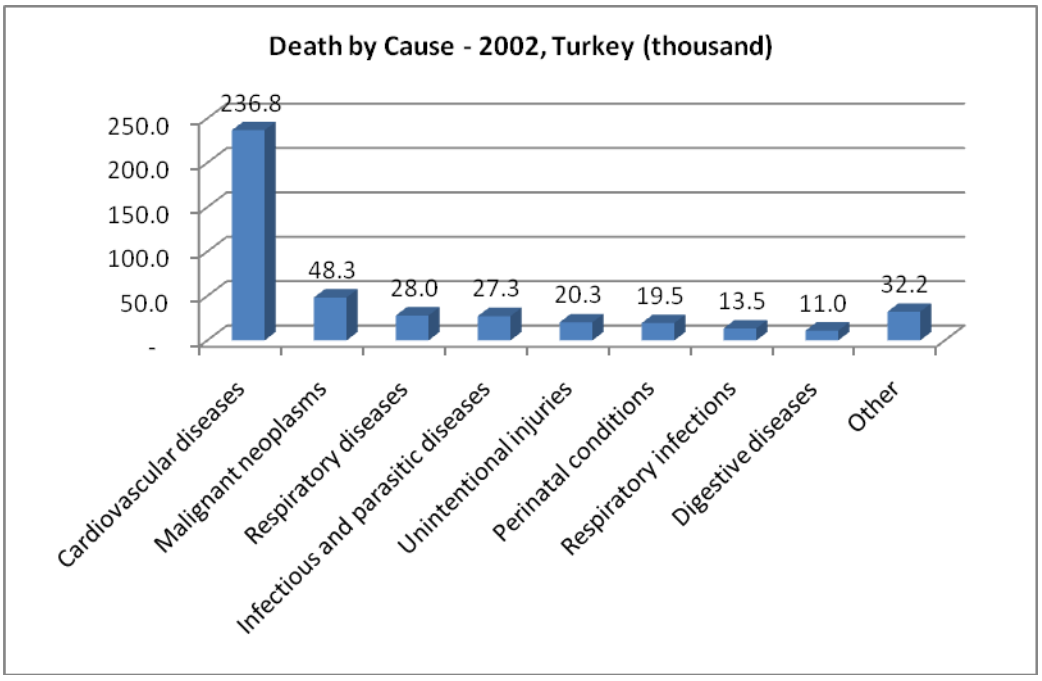

Figure 2: Death by Cause - 2002, Turkey
www.ketem.org, 2010

Cancer early diagnosis, screening and treatment center in Turkey made a research among 8 cities (Ankara, Antalya, Samsun, Erzurum, Trabzon, İzmir, Edirne, Eskişehir) from different regions of Turkey corresponding to 20 % of all population and kept records for cancer incidence rates since 1999. The Figure 3 below displays the development of cancer incidence rates from 1999 to 2005. It illustrates that from 1999 to 2005 incidence rate increased steadily from 58.13 to 173.85 per 100.000 people. The increase is cancer incidence rate is drastic as it

tripled in 6 years. This demonstrates that burden of cancer is increasing each year making public authorities obligated to take action against it for overall wellness of society.

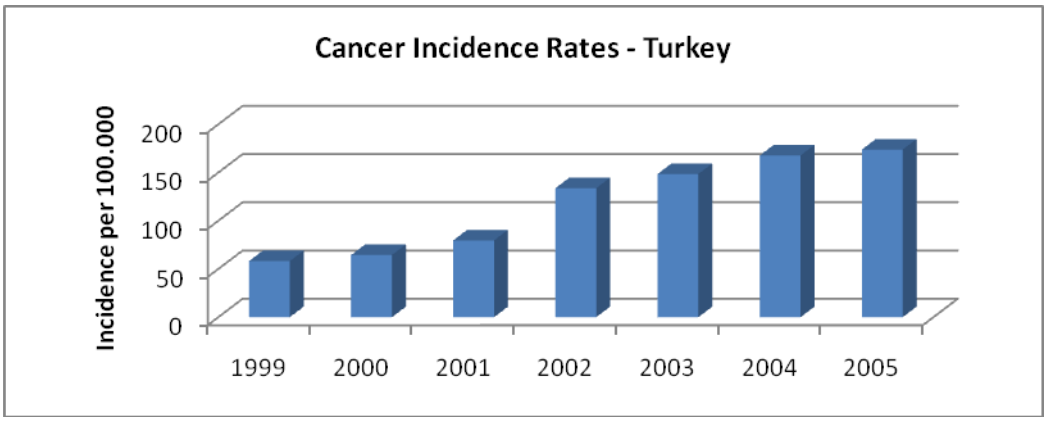

Figure 3: Cancer Incidence Rates - Turkey
www.ketem.org

The main types of cancer leading to overall cancer mortality among the world each year are (WHO, 2004):

- lung (1.3 million deaths/year)
- stomach (803 000 deaths)
- colorectal (639 000 deaths)
- liver (610 000 deaths)
- breast (519 000 deaths)

Deaths caused by each cancer type according to gender are illustrated below in Figure 4. The most frequent types of cancer worldwide (in order of the number of global deaths) are:

- Among men - lung, stomach, liver, colorectal, oesophagus and prostate
- Among women - breast, lung, stomach, colorectal and cervical

Breast cancer is the top cancer in women worldwide and is increasing particularly in developing countries where the majority of cases are diagnosed in

late stages. It was estimated that 636,000 incident cases occurred in developed countries and 514,000 in developing countries during 2002.

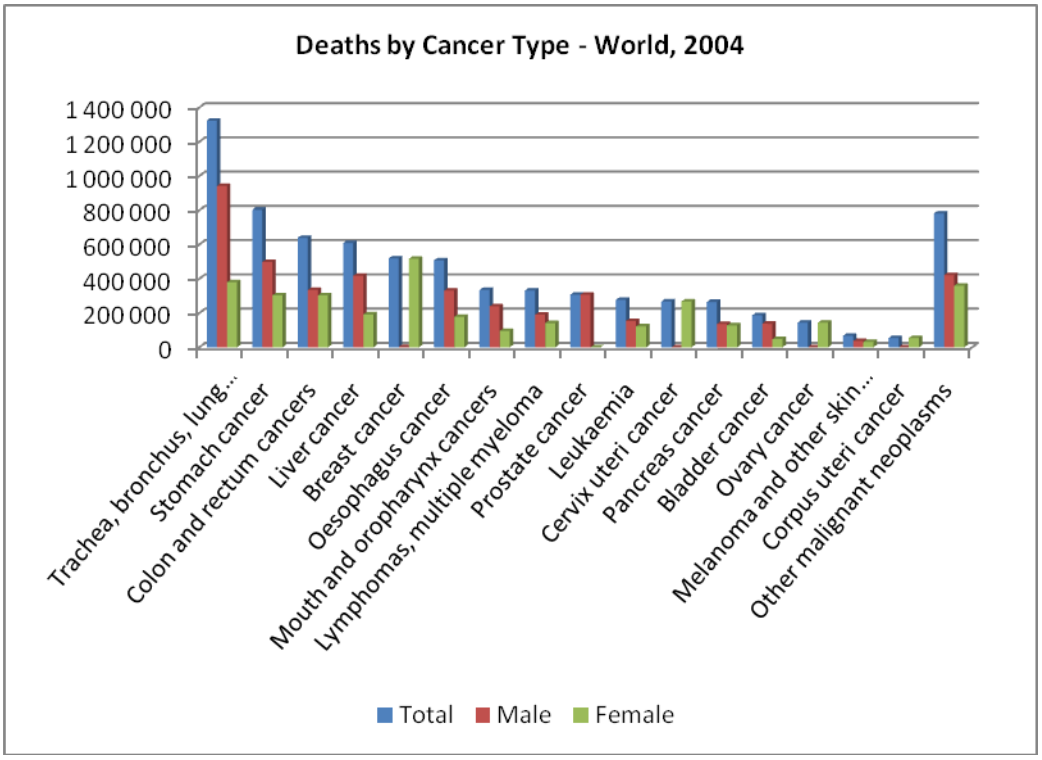

Figure 4: Deaths by Cancer Type - World, 2004
WHO, 2004

Breast cancer is also the most important cause of neoplastic deaths among women; the estimated number of deaths in 2002 was 410,000 worldwide. The number of deaths in 2004 is estimated as 519,000 by WHO for 2004. (Boyle, et al., 2008)

Although breast cancer is thought to be a disease of the developed world, a majority (69%) of all breast cancer deaths occurs in developing countries. Figure 5 illustrates the incidence and mortality rates in females by cancer type in income groups.

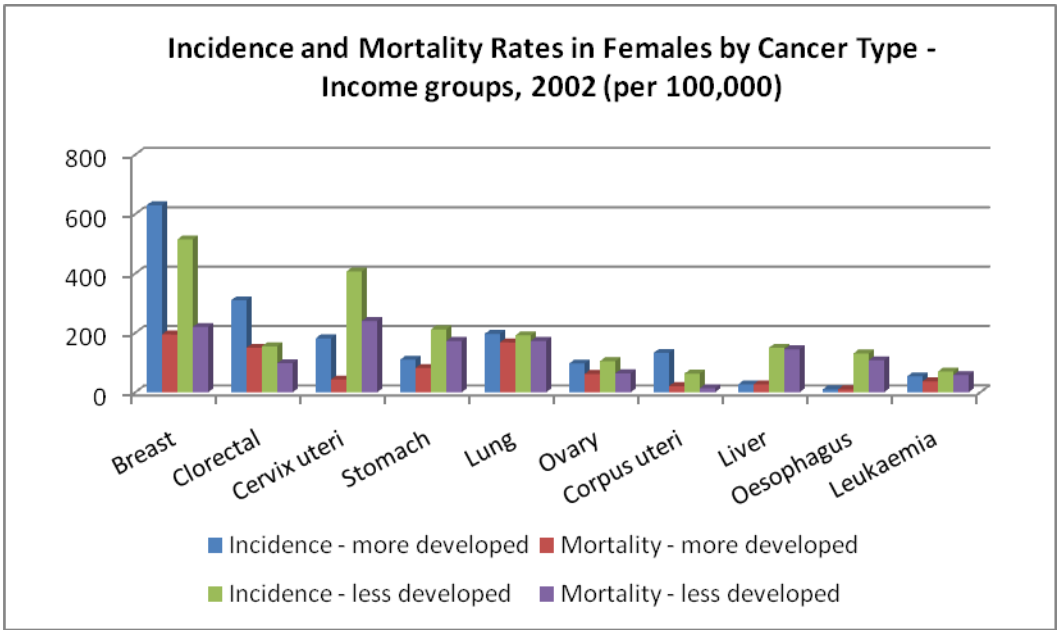

Figure 5: Incidence and Mortality Rates in Females by Cancer Type - Income groups, 2002 (per 100,000)
(Boyle, et al., 2008)

Exact causes of breast cancer are not known. Even there are some certain risk factors such as;

- Age
- Personal History
- Family History
- Genetic Alterations:
- Reproductive and Menstrual History
- Race
- Radiation therapy to chest
- DES (Diethylstilbestrol
- Obesity
- Alcohol.
- Oral contraceptives and hormonal replacement therapy

when a woman develops breast cancer the physician examining her seldom realizes the reasons behind cancer formation. Most of the risk factors of risk factors, such as age, genetic alterations etc., are unavoidable. Therefore in order to cope with breast cancer instead of fighting with risk factors, fighting with the disease itself is necessary.

Breast cancer is a progressive disease and it needs some time before it gets hazardous. It is separated into stages, by a specific method called TNM classification, according to the progress it has made. TNM classified stages of breast cancer are as follows;

- Stage 0
- Stage I
- Stage IIA
- Stage IIB
- Stage IIIA
- Stage IIIB
- Stage IIIC
- Stage IV

Staging is extremely important in breast cancer because many variables are dependent on the stage that the disease is diagnosed. Once the disease is diagnosed in early stages, survival rates of the patients and economical resources spent on the treatment and rehabilitation processes will be lower. Moreover lack of economical activity because of labor force lost and life quality lost due to breast cancer will be lower in earlier diagnosed cases as well.

Diagnosing breast cancer in early stages can best be done by randomly checking women who do not have clinical symptoms of breast cancer for a possible breast cancer occasion, which is called screening. Breast cancer screening can be done by clinical and self breast exams, mammography, genetic screening, ultrasound,

and magnetic resonance imaging. The most widely used approach is the mammography screening.

This study endeavors to analyze the possible economical effects of a population based mammography screening program for Turkey. Once a population based screening program is applied, the breast cancer incidences will be diagnosed in earlier stages, and thus economical resources spent in the treatment and rehabilitation processes will be lower as well as the economical activity lost due to the disease. The burden of such a screening program, on the other hand, will be cost of mammography screening and the further medical intervention costs resulting from abnormal mammograms.

Besides seeking answer to the question, whether a population based screening program would be cost-effective in terms of economical considerations, there are two more issues that this study aims to discover. First, what should be the minimum age for a woman to be included in the screening program, and second, how often should a woman be subject to screening for economical efficiency.

2 BURDEN OF BREAST CANCER

Breast cancer is the leading cause of death among all cancer types among women and there have been 516,644 deaths occurred in 2004 (http://www.who.int, 2010). Besides, future projections about the burden of breast cancer state that the burden of the breast cancer in terms of incidence and mortality rates will be even higher. It is predicted that the number of deaths due to breast cancer will increase to 787,041 by the year 2030. (http://www.who.int, 2010) However, the burden of breast cancer on the society is not limited to the mortality. There is also an economical burden of the disease, resulting from treatment and rehabilitation processes, and the lack of economical activity due to labor force lost.

David Radice et al. searched for the detailed burden of breast cancer in terms of direct and indirect costs. (Radice, et al., 2003) The worldwide economic burden of breast cancer in 2001 was projected to be in the range of $US300–400 billion ($US100–140 billion as direct costs). In the last decade, an overall $US500 billion was spent to treat this deadly disease. Table 1 and Table 2 show the estimated total and per-patient direct and indirect costs of stage III and IV breast cancer for the year 1995 in the US (unpublished data, Decision Resources Inc.). Direct costs are physician visiting costs, diagnostic costs, radiation therapy and drug costs, surgery costs and the costs of home health care visits. The detailed cost estimations for USA for stage III and IV breast cancer in 1995 are summarized in Table 1.

Table 1: Estimated Total Direct Costs of Breast Cancer

Item	Total direct cost ($US; 1995 values)	
	stage III	stage IV
Physician visits	27 300 000	25 602 675
Mammography	4 285 809	1 866 125
Biopsy	4 018 560	7 607 652
Bone scan	669 760	1 267 942
Chest x-ray	384 210	1 394 105
CAT scan	1 839 368	5 133 956
Liver CT scan	2 899 224	5 488 604
MRI scan	4 096 225	15 434 799
Drug therapy	42 000 000	114 000 000
Mastectomy/other surgery	110 112 750	133 794 703
Radiotherapy	4 950 000	9 265 730
Bone marrow transplantation	NA	260 172 920
Hospice care	NA	84 651 000
Home healthcare	78 825 600	98 532 000
Total direct costs	**281 377 506**	**764 212 211**

CAT = computerised axial tomography; **CT** = computed tomography; **MRI** = magnetic resonance imaging; **NA** = not applicable.

(Radice, et al., 2003)

Indirect costs for stage III and stage IV were estimated according to the 1995 Statistical Abstract of the United States and the International Monetary Fund. Indirect costs for stage III breast cancer were estimated considering the 1995 incidence (16 500) multiplied by the expected workforce rate, which varies by age cohort, and then multiplied by the actual workforce rate (15–25% depending on age). The total number of days lost for the incident population has been calculated by multiplying the non-workforce population by a total of 125 days (to account for an expected half year of missed work). Assuming that those who are kept out of the workforce by the disease are inactive for the entire year (250 days), the resulting number of lost days totals nearly 2 million. Combining this figure with the number of missed days from work and the incident population results in more than 2.7 million days of missed work.

Table 2: Estimated Total Indirect Cost of Breast Cancer

Item	Estimated indirect costs ($US; 1995 values)	
	stage III	stage IV
Missed days of work (A)	2 727 002	310 750
Missed days of work due to mortality (B)	NA	5 166 500
Total (C = A + B)	2 727 002	5 477 250
Cost of a missed day of work (D) [$US]	111	111
Total indirect cost (C × D) [$US]	302 697 222	607 974 750

NA = not available.

(Radice, et al., 2003)

Table 3 below illustrates the initial, continuing and terminal care costs for breast cancer patients tracked in USA with respect to diagnoses stage of their breast cancer, age distribution and co morbidity rates. The figures show that all of the initial, continuing and terminal care costs are highly related with the stage of the breast cancer when the disease is diagnosed. Especially continuing care costs are much higher in distant breast cancer, with respect to other stages. Costs of breast cancer care are also dependent to age at diagnoses and co morbidity.

Table 3: Costs for Breast Cancer by Stage

	Initial care			Continuing care			Terminal care		
	n	cost	SE	n	cost	SE	n	cost	SE
Total no. of patients	645	10 813	224	2111	1084	36	187	17 686	1399
Stage									
CIS	86	8 515	602	212	888	113	10	11 222	6054
Local	390	10 835	277	1309	958	45	74	14 962	2179
Regional	150	12 273	451	545	1423	70	74	20 323	2199
Distant	8			23	2921	388	22	20 610	4158
Unknown	11			22	1308	349	7	18 630	7759
Age (years)									
35–49	187	11 791	411	367	1078	89	20	28 196	4053
50–64	185	11 159	417	626	991	65	47	21 426	2684
65–79	225	10 054	373	903	1104	54	81	16 857	2041
≥80	48	9 135	797	215	1353	113	39	9 937	2945
Comorbidity[a]									
Low	262	10 577	347	758	684	56	28	17 354	3575
Medium	175	10 712	425	673	1091	59	47	15 859	2818
High	94	11 053	590	559	1543	65	107	18 812	1861

a The number of patients with comorbidity does not match the total number of patients because when breast cancer is in early stages roughly 30% of patients do not have concomitant additional diseases.

CIS = carcinoma *in situ*; **SE** = standard error.

(Radice, et **al**., 2003)

3 SCREENING FOR BREAST CANCER

Breast cancer screening is a test applied to women known as breast cancer free in order to achieve early diagnosis. The aim in screening is to diagnose the disease in earlier stages and reduce mortality and disability rates as well as the treatment costs. (http://en.wikipedia.org, 2010) The methods of screening are clinical and self breast exams, mammography, genetic screening, ultrasound, and magnetic resonance imaging. Breast exams include feeling the breast for abnormalities, whereas mammography screening is taking regular mammograms. Ultrasound and magnetic resonance imaging are not breast cancer screening methodologies; instead they are supplementary tools for screening.

Unlike other cancer types, breast cancer is not a risk factor dependent disease. There is no changeable environmental risk factor that is attached to breast cancer probability. If it was so, controlling that risk factor would mean controlling breast cancer. For instance, lung cancer burden can be controlled by controlling the tobacco usage since it is the main risk factor of lung cancer. Similarly, stomach cancer can be averted by controlling the diet. However, there is no such risk factor behind breast cancer that is controlling it would mean controlling breast cancer. Breast cancer mortality and burden of breast cancer can be controlled not by controlling incidence rate; instead it can be controlled by early diagnosis and early diagnosis can only be possible by screening. Breast cancer screening is effective because breast cancer is a slowly developing progressive disease. By regular screenings it is possible to detect the disease in early stages.

Effects of breast cancer screening in mortality reductions are tested in some randomized trials in different countries. Outcomes of these trials are discussed below.

3.1 Randomized Trials

In order to reliably estimate the effectiveness of screening around the world there has been made large randomized clinical trials involving approximately 650,000 women in North America and Europe namely; Canada1980; Edinburgh 1978; Göteborg 1982;Malmö 1976; New York 1963; Stockholm 1981 and Two-County 1977. Women without previously diagnosed breast cancer are subjected to these randomized trials. They are separated into two groups; one is the experiment group and the other is the control group. Women in experiment group were exposed to screening with mammography with the interval of one or two years, whereas the women in control group were not examined by mammography screening. Both women in two groups are followed by 13 to 20 years. The time horizon that the women are followed in each trial and applied screening methodology is given in Table 4.

Table 4: Randomized Trials

Trial	Year	Age	Screening Interval	Participation	Time Horizon
Canada	1980	40-59	1 year	50,430	13 year
Edinburgh	1978	45-64	2 year	44,268	13 year
Göteborg	1982	39-59	18 months	51,611	14
Malmö	1976	43-70	18 months	60,076	16
New York	1963	40-64	1 year	60,995	18
Stockholm	1981	40-64	28 months	60,117	15
Two Country	1977	40-74	2 year	133,065	20

Source: (Getzche, et al., 2009)

After this defined follow up period experiment group is compared with the control group in measuring the outcomes as mortality from breast cancer, mortality from any cancer, all-cause mortality, use of surgical interventions, use

of adjuvant therapy and harms of mammography. As a result of these trials significant reduction in breast cancer mortality rates were realized. Biggest reduction in breast cancer mortality is faced in New York trial as 35 %, followed by 24 % mortality reduction in Two Country trial. Similar mortality reductions were obtained in other trials between 15% and 35%. Best results were obtained for the women having their first mammography after the age of 50. (Getzche, et al., 2009)

4 LITERATURE ON COST-EFFECTIVENESS OF BREAST CANCER SCREENING

Effectiveness studies about breast cancer in literature are usually from a medical point of view and only mortality reductions due to breast cancer screening program is considered and cost considerations are discarded. There are few studies in the literature aiming to estimate cost-effectiveness of breast cancer screening programs as well as seeking the optimal screening strategy. Those studies guide this thesis throughout the development of the model constructed in terms of aim, methodology and data sources.

First aspect of the model that needs guidance is the determination of the exact goal. The primary objective and alternative scenarios should be clearly defined and the rest of the model should be constructed consistent with this objective. Similar studies in the literature have more or less the same primary objective; instead they vary on the alternative scenarios tested.

A study done in Slovenia by Rojnik et al. (Rojnik, et al., 2008) tries to determine the most cost-effective screening policy for population-based mammography breast cancer screening. It emphasize the importance of breast cancer for Slovenia with around 100 newly diagnosed cases per 100,000 women in a year and it will afflict 1 in 15 Slovenian women by the age of 75 years. Then it searches for the most effective population based screening policy that minimizes the total screening and treatment costs. 36 alternative scenarios is included in the study varying in terms of age distribution of the women that will be subject to screening, from 40 to 80, and the screening interval to be implemented, annual, biennial and triennial.

The objective of the model in another study conducted by Yılmaz and Yazıhan (Yılmaz, et al., 2007), on the other hand, is more deterministic and simplistic. It tries to analyze whether implementing a population based screening program including women aged between 50 and 70 would be beneficial in terms of economic efficiency. It does not include any alternative scenarios and has just one question to answer; that is whether the costs of screening each woman over 50 biennially would be lower than the benefits of such a program, in terms of reduced treatment costs due to early diagnosis.

Another study searching the economic efficiency of breast cancer screening is carried out in Japan among women aged between 30 and 70 (Ohnuki, et al., 2006). The main objective of this study is quite different from the others. Instead of just searching economic efficiency of mammography screening among different age groups, it also compares the economic efficiency of different screening methods. These methods include the clinical breast examination alone, mammography screening, clinical breast examination with breast cancer screening and no screening. Again several scenarios are included with respect to age distribution and screening interval. Annual and biennial strategies among women aged between 30 and 70 are tested for all screening methods.

Final study in literature guiding this thesis in determination of the objective and alternative scenarios to be tested is the one done by Wong et al (Wong, et al., 2007) in China. It aims to evaluate if it is cost-effective to implement a population based mammography screening program among Chinese women between ages 40 and 79. Only biennial strategy is included and five different age groups are constructed to test for the optimal screening age.

After determining the objective and alternative scenarios to be implemented, methodology for testing those scenarios should be chosen under the constraint of

available data. Different studies in the literature consist of different methodologies for testing the cost-effectiveness, such as state transition Markov model, simulation model or deterministic model.

The study done by Rojnik et al. (Rojnik, et al., 2008) uses a time dependent Markov model to compare hypothetic populations of women, one followed clinically without screening and the others undergo different screening mammography policies. In classification of the breast cancer into stages TNM (Tumor Node Metastasis) classification is used. Women with breast cancer are allocated into 4 stages, namely; DCIS (ductal carcinoma in stu), Local, Regional and Distant. Structure of the model for breast cancer screening with the possible courses of the disease is as shown in Figure 6.

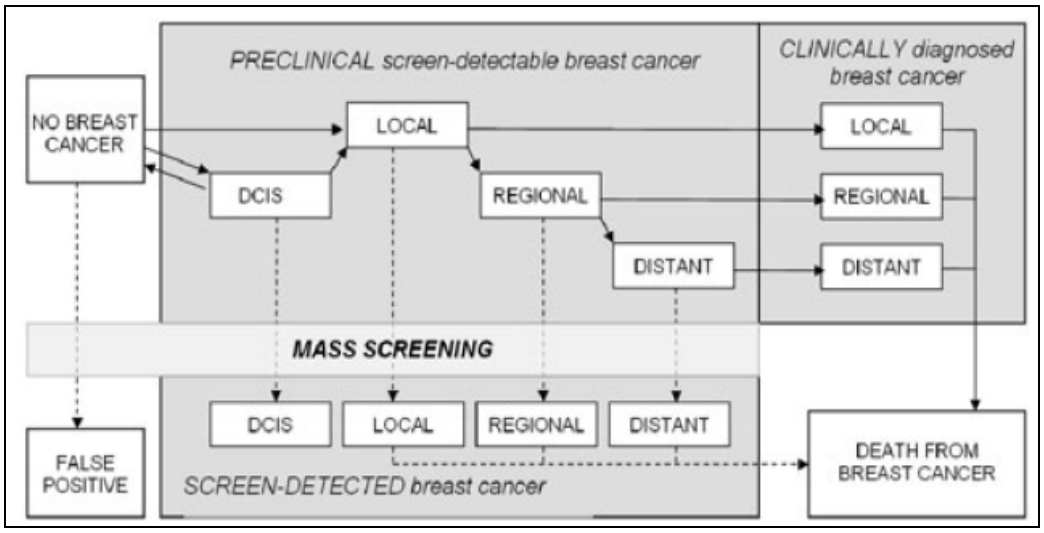

Figure 6: Modeling used by Rojnik et al.
(Rojnik, et al., 2008)

Breast cancer incidence, mammography sensitivity, mortality, and breast cancer relative survival are modeled as time dependent transition probabilities. The dashed lines correspond to transitions possible only by screening policies. The state "death from other causes" which can be attained from all other states is not shown. The transitions to clinically diagnosed local, regional, and distant states are governed by the rate of the incidence, clinical-stage distribution data, and

sojourn time. In the case of early detection by screening, the women enter the corresponding screen detected DCIS, local, regional, or distant states. The state "false positives" refers to women with positive screening examination in whom no breast cancer is found at further invasive assessment. The two absorbing end-states of the model are death from breast cancer and death from other causes.
This cohort simulation approach is run with a cycle length of 1 week for running the Markov model for 36 different screening policies with respect to two parameters, age and screening interval.

The methodology used by Yılmaz et al. (Yılmaz, et al., 2007) in calculating the total of screening and treatment costs for a population based screening policy is rather deterministic. First the number of patients with breast cancer, using the population projections between years 2007-2012 is predicted. Then screening cost for a patient using the detailed expenditure data gathered from "Cancer Early Diagnosis and Treatment Centers" is calculated. The total screening costs of the population under risk for a screening interval of two years is computed. Afterwards, the possible costs of treatment in no screening and with screening cases with respect to difference in the stage that the disease is diagnosed are calculated. Finally, the net present value of the total costs for 6 years is calculated and the possible savings of the projected breast cancer screening program are discovered.

The study done by Ohnuki et al. (Ohnuki, et al., 2006), on the other hand, includes a simulation model for calculating the cost-effectiveness of different breast cancer screening methodologies under several scenarios. The modeling is illustrated in Figure 7 below. In a theoretical cohort, 100 000 subjects participate in the first screening. Resubmitting those who do not contract breast cancer to the next screening (excluding those who dies of other diseases) by simulation allows the calculation of costs and effects for participation in screening at any age (for

example, from 30 to 79 years). Difference in the effects of annual and biennial screening emerges in the rate of false-negative breast cancers. It is hypothesized that the proportion of early stage breast cancers among women with a false-negative screening result would be similar to that among women who are not screened. The simulation is run for 15 years and projected costs and benefits are collected.

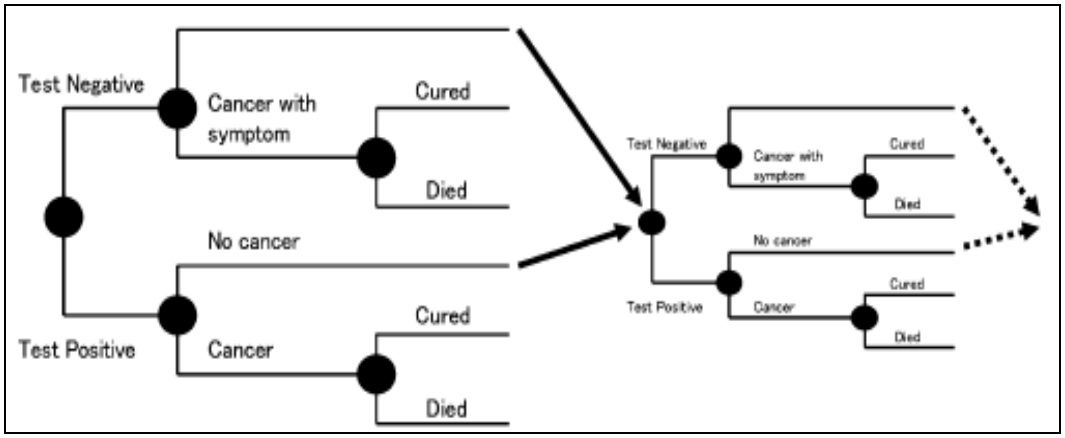

Figure 7: Modeling used by Ohnuki et al.
(Ohnuki, et al., 2006)

A state-transition Markov model, illustrated in Figure 8, to simulate biennial mammography, breast cancer diagnosis, and treatment in a hypothetical, population based cohort of Hong Kong Chinese women is developed in the study of Wong et al. (Wong, et al., 2007). Nodes of the Markov model are defined as ductal carcinoma in stu and 4 stages of the breast cancer classified in TNM classification. Also one source node as alive without breast cancer and two terminating nodes as deaths of breast cancer and deaths from other sources were included. The effectiveness of mammography is included by assuming that some cancers would be detected by screening at a less advanced stage compared with no screening. For newly diagnosed cancers in unscreened women local stage distribution is applied and for newly diagnosed cancers in screened women the stage distribution in SEER data from the U.S. is used to represent the stage shift caused by screening. Only biennial screening is evaluated. 5 different strategies;

no screening, biennial screening of women between ages 50-69, 50-79, 40-69 and 40-79 are compared in terms of life expectancy, quality adjusted life expectancy, and lifetime costs. The model is run for a time horizon of 50 years and the results are collected.

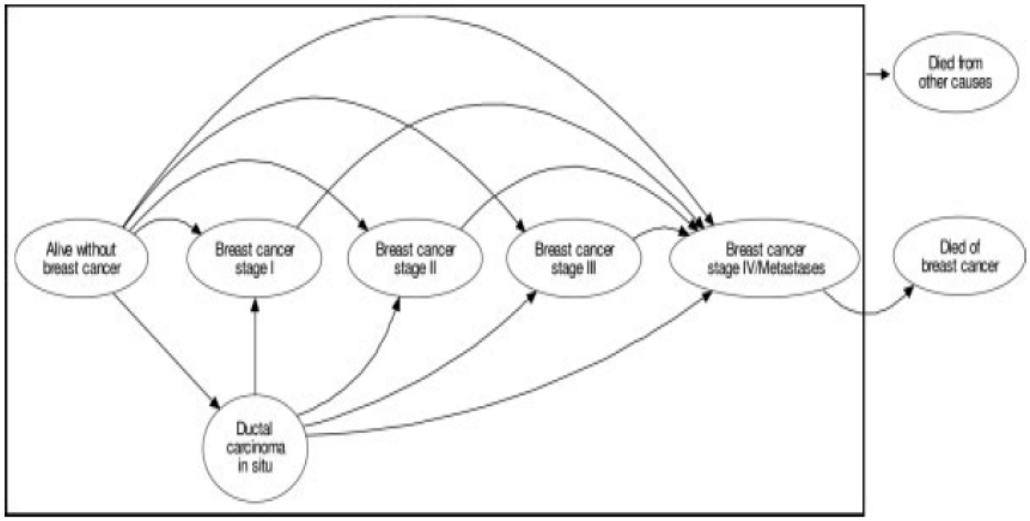

Figure 8: Modeling used by Wong et al (Wong, et al., 2007)

After constructing the model in the light of these studies in the literature the available data sources may be used in the thesis are searched among those studies. All data regarding age-dependent cancer incidence, clinical-stage distribution, treatments, and survival rates are obtained from the Cancer Registry of Slovenia in the study of Rojnik et al. (Rojnik, et al., 2008) The costs for mammography examination, the costs for diagnostic interventions for clinically detected breast cancer, the costs for invasive and noninvasive diagnostics at recall, and the costs for treatment interventions are obtained from the Institute of Oncology Ljubljana. QALYs for treatment and the corresponding durations of treatments are obtained from the literature. The quality of life for DCIS, local and regional breast cancers after treatment is weighted according to the treatment interventions. The quality of life for distant cancer is weighted with 0.515. The quality of life for women with false positive result is also reduced according to

the diagnostic duration and QALY weight. In the case of death from breast cancer, a terminal illness lasting 1 month with QALY weight of 0.288 is taken into account.

Probable number of breast cancer cases in women at the age group 50+ in Turkey in general is calculated using the number of breast cancer cases obtained from screening results in Cancer Early Diagnosis and Treatment Centers and population projections in the study by Yılmaz et al. (Yılmaz, et al., 2007). Screening costs per patient is calculated by examining in detail the cost structures of Cancer Early Diagnosis and Screening Centers. The costs of surgical operation, radiotherapy and medicine treatments, and laboratory tests used in diagnosis and monitor, which are applied during the 14-57 months monitor period are calculated excluding the costs of line in hospital for 14 stage I, 6 stage II, 9 stage III, and 6 stage IV patients with adjustment to 2007 prices and hence treatment and monitor costs for patients in each stage are calculated as average annual costs.

For each of the screening strategies, sensitivity, specificity and proportion of early stage breast cancer are derived from studies conducted in Miyagi prefecture in the study done by Ohnuki et al. (Ohnuki, et al., 2006) Mortality from breast cancer and total mortality are derived from the annual report on Vital Statistics of Japan in 2001, and life expectancy is derived from the 19th Life Table. The proportion of early stage breast cancers among breast cancers detected at outpatient departments, the 5-year survival rate by clinical stage, screening costs, further examination costs, diagnostic costs for outpatients and treatment costs are based on a questionnaire survey carried out by the Grant-in-Aid for Cancer Research from the Ministry of Health and Welfare in 1996 at 13 institutions in Japan.

In the study done by Wong et al. (Wong, et al., 2007) age-specific invasive breast cancer incidence and associated stage distribution are obtained from the Hong Kong Cancer Registry. Because DCIS incidence is not recorded locally, the age specific proportions of DCIS are adopted among all newly diagnosed breast cancer cases in the Surveillance, Epidemiology, and End Results (SEER) data in 1983 and 1998 for the unscreened and screened women in the model, respectively. All- cause mortality is abstracted form local data. Cost estimates are derived from local public sector costs and private sector charges. Transition probabilities are calibrated according to the observed 5-year relative survival statistics from the SEER data for stages I, II, and III from the most recent 15 years. For stage IV or metastatic disease cancer specific death rates are derived from the relative survival data from patients with stage IV disease. Quality adjusted life years are weighted according to stages of breast cancer as 0.95, 0.9, 0.8, 0.7, and 0.3 respectively for DCIS, Stage I, II, III and IV.

Results of the all these four studies in the literature, favors breast cancer screening against no screening. Based on commonly quoted thresholds of society's willingness to pay per QALY in Slovenia, the policy of choice for breast cancer screening in the Slovenian population is found as screening women aged from 40 to 80 years every 3 years in the study of Rojnik e al. (Rojnik, et al., 2008). The savings achieved in treatment expenditures for six years is calculated as 217.78 million YTL for Turkey by Yılmaz and Yazıhan (Yılmaz, et al., 2007) if the total female population under risk is to be screened once two years. In all age groups, the smallest ratio of cost to survival duration is observed for biennial clinical breast examination and mammography screening together in Japanese case (Ohnuki, et al., 2006) and of the 5 strategies considered biennial mammography for all women ages 40 years to 69 years is found out as the least

costly, non-dominated screening option among Chinese women. (Wong, et al., 2007)

5 COST EFFECTIVENESS ANALYSIS MODEL FOR TURKEY

5.1 Aim

It is now clear that breast cancer has great burden on the society in both economic and social aspects and cannot be left to competitive markets for the optimal allocation to be stored. Governments should intervene in the market and make a public choice for providing optimality. It is also clear that breast cancer is not a disease that is dependent on the amendable factors. In other words unlike most of the other diseases, breast cancer cannot be averted by controlling risk factors because main factors such as age and genetic structure are not controllable. For example, while policies against tobacco usage may result in serious decrease in lung cancer, or a change in diet may decrease the incidence rate of stomach cancer, there is no such thing known that can affect the incidence rate of breast cancer. (www.who.org, 2010) The only way to struggle with breast cancer is to diagnose it in early stages, before it spreads all over the body. Early diagnosis of the breast cancer can only be done by mammography or ultrasound screenings. Hence, in struggle with breast cancer governments should implement screening programs to provide diagnosis of the breast cancer before spreading and reduce the overall burden of the breast cancer to the society.

It is for sure that a population based screening program would decrease the amount of resources spent in the treatment of breast cancer, because early detected cases are cheaper to treat in terms of treatment methodology used. A screening policy is also expected to decrease mortality rates and disabilities caused by breast cancer, because earlier diagnosis of the cancer means greater survival rates and less distortion to the patient in the treatment process.

However, screening program charges extra burden on the society in terms of resources spent during the screening process. These resources include both the investments needed for screening the women in the risk group and the further operational costs about clarification of the status of the cases resulted from abnormal screenings. The question here is that whether the decrease in the treatment costs, mortality rates and disability rates are enough to compensate the screening costs and operational costs resulted from abnormal screenings. In other words, would a prospective population based screening program is cost effective.

The aim of the model constructed in this study is to answer this question for Turkey and find out if a population based screening program would have positive effect on the resources spent for breast cancer. Population based screening program is tested for cost effectiveness by the model. However, the aim is not limited to measuring cost effectiveness. The optimal screening strategy in terms of mortality and disability rates, screening costs and treatment costs is investigated as well. The screening strategies determined according to two criteria, minimum age to screen and frequency of screening, are compared to find out which screening policy would be most effective. At the end of the study the questions;

- Whether a population based screening program is cost-effective
- What is the optimal minimum age for screening
- What is the optimal screening interval

are expected to be answered.

5.2 Model

For finding answers to questions in the previous section a real-world simulation model is used. All the components of a breast cancer screening program are

transferred to simulation software, Arena 4.0, and using Markov analysis logic several strategies tested for cost effectiveness. Basically each single woman in real world is treated as an entity strolling between nodes in the simulation model and all possible states that a woman can be in are constructed as the nodes to be strolled. Transition probabilities between these nodes are estimated from real world applications, some of which existed in the literature or databases, and some of which are derived from surveys conducted or from hospital records. The databases of World Bank, World Health Organization, International Money Fund, Turkish Institute of Statistics and Turkish Republic Ministry of Health, survey results from Cancer Early Diagnoses and Treatment Centers from different districts of Turkey, namely Antalya, Kayseri, Ankara, Ordu, Denizli, Konya, Bursa, Balıkesir, Sivas, and hospital records of Aegen University Hospital and Ankara Numune Hospital are used in the estimation of transition probabilities. Estimation of each variable used in the model is explained in detail in the following sections.

Structure of the model is illustrated in Figures 9 and 10. Each of these figures presents a single closed sub-model that make up the whole model together. First sub-model (Figure 9) includes the period between a woman entering the system and it is diagnosed by breast cancer and transferred to the treatment sub-model. Second sub-model includes the period from the beginning of the treatment to the time the women leaves the system, i.e. die.

In the screening sub-model, first of all, women population over 30 according to the last census done by Turkish Institute of Statistics in 2008 is created as unique entities at the beginning of the simulation. This is the only entity creation throughout the simulation. Although the risk group for breast cancer is chosen as women between 40 - 70 years, an entity created for each female over 30 by the thought that in 10 years time, which is the simulation length, females between 30

and 40 years old will be added to the risk group. After creation of the entities they are marked with an attribute defining their ages.

Entities are then transferred to the decision node where screening decision is made according to the screening strategy given and the value of their attributes. According to the decision made entities are sent to "screened" or "unscreened" nodes.

In the screened node according to the transition probability derived from the survey results coming from Cancer Early Diagnosis and Treatment Centers the entities are dispatched to positive or negative nodes implying the result of the screening. From negative node there are two paths that an entity can follow, it is either be transferred to the terminating node meaning that the person dies or it is transferred back to the decision node after age attribute is increased by one for the next year's decision. This choice is done according to the transition probability derived from the mortality rate data of Turkish Institute of Statistics for 2008.

Entities in the positive node, on the other hand, are separated into false positives and true positives nodes according to the age dependent mammogram specificity rates taken from literature. Entities in the false positive node are treated similar to the ones in negative node. They are either disposed according to the mortality rates, or transferred back to the decision node by increasing age by one for the next year's decision. An entity in the true positive node represents a women actually diagnosed by breast cancer and the stage of the cancer should be decided. Therefore according to the survey results from Cancer Early Diagnosis and Treatment Centers and value of the age attribute they are dispatched to the stage nodes from Stage I to Stage IV. Then, entities in the stage nodes left the screening sub-model and transferred to the treatment sub-model.

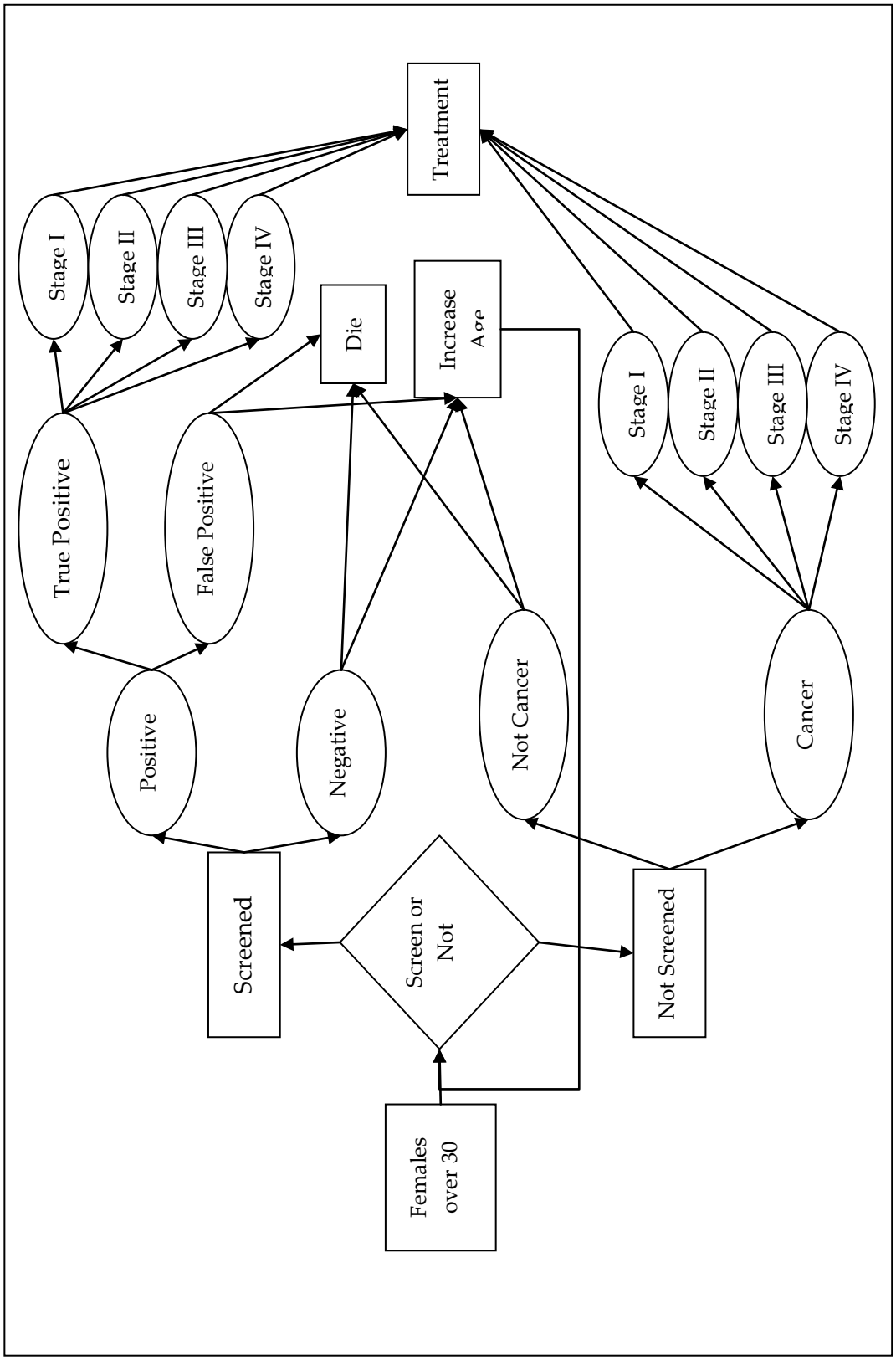

Figure 9: Sub-Model Screening

In the unscreened node according to the transition probabilities derived from survey results, entities are transferred to the "clinically diagnosed breast cancer cases" node or "not breast cancer" node. Entities in the "not breast cancer" node are the dispatched to the disposing node or age increase node according to the mortality rate data similar to the entities in the false positive or negative nodes. Entities in the "clinically diagnosed" node, on the other hand, are transferred to the treatment node after stages of the breast cancer for each entity is determined according to the transition probability derived from the hospital records of Aegean University Hospital and Ankara Numune Hospital.

Entities coming to treatment sub-model are dispatched into two paths. They are either sent to "die due to breast cancer" or "not die to due to breast cancer" nodes according to breast cancer survival rates taken from the literature. Entities transferred to "die due to breast cancer" node are done sent to "death burden" node but they are not disposed yet. Those entities enter in a loop between "death burden" and "age increase". This is done to keep record of the death burden due to breast cancer.

Entities keep looping until they are completely disposed by the probability of mortality rate due to another reason. This loop provides the accurate calculation of the death burden.

Entities transferred to "not die due to breast cancer" node are disposed by the probability derived from mortality rate data. If an entity in "not die due to breast cancer" node is not disposed, in other words, if a women taking breast cancer treatment does not die, it is transferred back to treatment node for the following years of treatment.

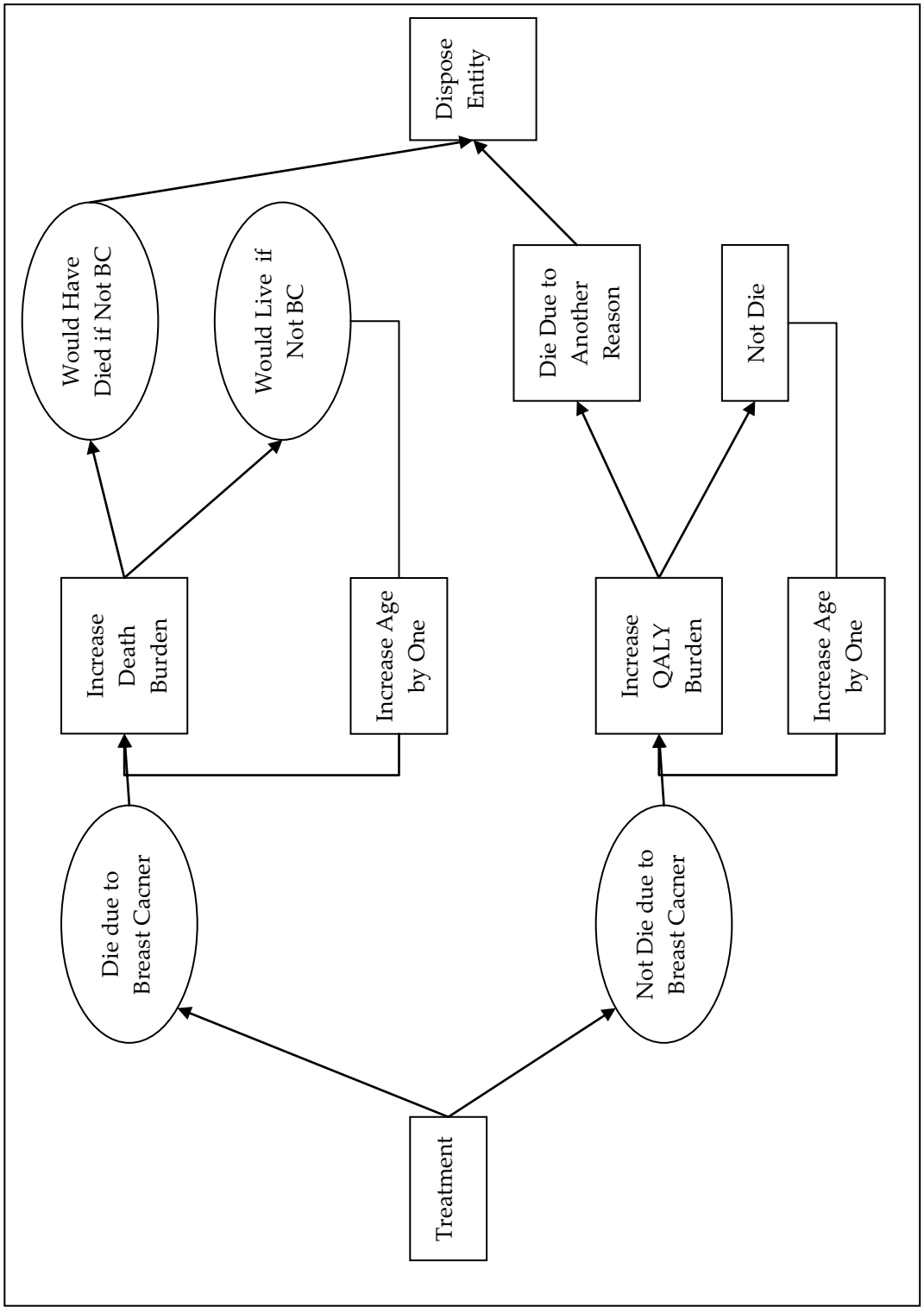

Figure 10: Sub-Model Treatment

Transition probabilities changes for each entity in each loop according to some factors such as age, screening strategy applied and whether the patient is previously screened or not.

At each node visited by an entity corresponding outputs are kept for each year. For example, when a stage III breast cancer patient entity visits the treatment node, corresponding treatment cost is incurred. Similarly, when an entity visits the false positive node, number of false positives and corresponding false positive costs are increased by their values. These outputs are then summarized and classified in order to make appropriate analysis. The results of the simulation are discussed in the following section.

10 different screening methodologies and 1 base scenario are applied to collect results, and to compare the effects of different strategies. These strategies are chosen according to the similar studies in the literature, under the constraint of the data that can be reached. These strategies consist of 5 annual screening strategies and 5 biennial screening strategies according minimum age to be screened, which are 40+, 45+, 50+, 55+, and 60+.

5.3 Data

5.3.1 Estimation of Target Population

To run a simulation model for discovering the benefits of a population-based breast cancer screening policy, first thing needed to know is the number of women to be included in simulation each year. Once the target population to be included is estimated, this number can be used as the number of entities to be created in the simulation model. Those entities will stroll around the simulation nodes by specific transition probabilities and build-up the total cost and benefit values. The main parameter in the simulation is the age group, since breast cancer incidence rates are very much dependent on the age. Therefore, besides

estimation of the target population to be included in simulations, age of each entity should also be determined. Ages of women can be thought as attributes of entities that will be used during simulation, provided that they will be updated each simulation year.

Instead of a deterministic calculation of the number of women in risk group for each year, a rather dynamic approach is used during simulations. At the very beginning of each simulation, all entities are created once and for all according to the results of the "abode based census". Table 5 displays the results of the 2009 census for all ages, as the number of entities to be created at the beginning of the simulation. However, rather than the age group of a woman in the simulation model, exact age should be known in order to update her age in each simulation year. Therefore, female population for each year should be further divided into unique ages. For simplicity, it is assumed that a given age group consists of equal number of females for each exact age. For instance, female population aged 47 is assumed to be 445,682 (2,228,411/5).

Table 5: Female Population in Turkey

Age Group	Female Population	Age Group	Female Population
30-34	2.912.568	50-54	1.847.369
35-39	2.740.457	55-59	1.483.667
40-44	2.296.915	60-64	1.236.594
45-49	2.228.411	65-69	920.652

Source: TUIK, 2009

After creation of all women as entities at the beginning of the simulation and exact ages are attributed to them, target population is estimated for the first simulation year. However, in order to estimate the target population for successive simulation years a specific transition probability is needed. That is the termination rates of the entities. At the end of each simulation period there are

two possibilities for each entity. It either will continue to the next simulation period by increasing the value of age attribute by one, or leave the system. In other words, at the end of each year, a woman will either continue to live by aging one more year, or die. Therefore, for estimating the target population in successive periods of the simulation, terminating probabilities of the entities, in other words mortality rates of the women, should be known. Table 6 illustrates the mortality rates for females according to the age groups, which is used as the transition probability of termination node. These rates are mortality rates of females excluding the deaths caused of breast cancer in 2009. Breast cancer mortality rates excluded from overall mortality rates, since they are used as separate transition probabilities, in order to prevent double counting.

Table 6: Mortality Rates Excluding Breast Cancer

Age Group	Mortality Rates*	Age Group	Mortality Rates*
30-34	0,0269%	**55-59**	0,2786%
35-39	0,0399%	**60-64**	0,4833%
40-44	0,0631%	**65-69**	0,8437%
45-49	0,1046%	**70-74**	1,5542%
50-54	0,1684%	**75+**	4,1512%

Source: TUIK, 2009

5.3.2 Probability of Breast Cancer

Probably the most crucial data in the simulation model for accurate calculation of the cost and benefits of breast cancer is to correctly estimate the probability for a woman to get cancer. The model then can be used to calculate the overall burden of the breast cancer in accordance with the estimated target population. The very basic way to estimate breast cancer probabilities is to look at the yearly incidence rates registered in previous years. These incidence rates can be considered as the probability for each individual to develop breast cancer.

Cancer Struggle Agency of the Ministry of Health made a study including 2004-2006 aiming to display the overall incidence rates for each cancer type. In the context of this study number of breast cancer cases taken from the eight different Cancer Registry Centers[1] in different cities of the country is divided by the overall female population of these cities in order to derive a breast cancer incidence rate. Breast cancer incidence rates for three consecutive years derived by Cancer Struggle Agency of the Ministry of Health are presented in Table 7.

Table 7: Breast Cancer Incidence Rates Estimated by Ministry of Health

	2004	2005	2006
Incidence Rate	0,0373%	0,0384%	0,0417%

Ministry of Health, 2007

According to the results of the study conducted in eight cities, breast cancer incidence rate appears to be about 39 in 100,000. However, there are strong shortcomings of this study in reflecting accurate incidence rates. First of all, breast cancer is a progressive disease and very much dependent on the age. Thus, an overall incidence rate derived by dividing the total number of cases to the population is quite pointless, since almost all of the breast cancer occurrences appear after the age of 40[2]. Another shortcoming of this exercise is that it is based on the data taken from the Cancer Registry Centers. It is for sure that Cancer Registry System of Turkey is not developed enough yet to be a data source for such a study. There may be a number of breast cancer cases diagnosed and under treatment in health facilities, however not registered to any Cancer Registry

[1] Antalya, Kayseri, Ordu, Denizli, Konya, Bursa, Balıkesir, Sivas

[2] Survey Results among Cancer Early Diagnosis and Treatment Centers

Centers. Moreover, there are also unknown breast cancer cases developing, which are not diagnosed yet.

In this thesis instead of using breast cancer incidence rates of the Cancer Struggle Agency of the Ministry of Health, more reliable incidence rates are calculated for the women over 40, according to the survey results coming from Cancer Early Diagnoses and Treatment Centers[3]. Number of mammography screenings between years 2007 to 2009, and number of breast cancer cases diagnosed in this mammography screenings are presented in Table 8. In 2007, 60 of every 10,000 women screened is found to be diagnosed with breast cancer, 82 of every 10,000 for 2008 and 67 of every 10,000 for 2009. These are more accurate breast cancer probability values including both registered and unregistered cases.

Table 8: Breast Cancer Incidence Rates Estimated Using Survey Results

	2007	**2008**	**2009**
No of Mammography Screening	37.274	35.866	24.639
Incidence	222	295	166
Incidence rate	0,60%	0,82%	0,67%

Source: Data Collected from Cancer Early Diagnosis and Treatment Centers

Using these incidence rates, probability for a woman diagnosed by breast cancer each year is calculated for each simulation period. However, since there are only three data points, doing trend analysis to predict future incidence rates is quite inappropriate, rather an average constant value is used. Overall breast cancer probability during simulation is used as 0.70 %, as the average incidence rate faced during random mammography screenings in Cancer Early Diagnoses and Treatment Centers.

[3]Antalya, Kayseri, Ordu, Denizli, Konya, Bursa, Balıkesir, Sivas

Overall breast cancer incidence rate is necessary data for running the simulation, but not a sufficient one. These overall incidence rates should be assigned to age groups. Table 9 displays the allocation of the 8,153 breast cancer incidences diagnosed between 2002 and 2006 in different health facilities into the age groups and relative frequencies of each age group.

Table 9: Breast Cancer Incidences Rates by Age Group

	40-44	45-49	50-54	55-59	60-64	65-69
2006	341	359	349	287	253	206
2005	288	324	332	281	243	169
2004	312	324	290	239	235	172
2003	371	311	263	227	211	180
2002	283	317	321	254	237	174
Total	1595	1635	1555	1288	1179	901
Relative Frequency	19.56%	20.05%	19.07%	15.80%	14.46%	11.05%

Source: Data Collected from Clinical Hospital Records[4]

By using these relative frequencies and with the assumption that the number of women screened in random screenings carried on Cancer Early Diagnoses and Treatment Centers are same for all age groups, age dependent cancer incidence rates can be calculated by the following formula.

$$Age\ Dependent\ Incidence\ Rate = Overall\ Incidence\ Rate\ X\ \frac{Relative\ Frequency}{\frac{1}{No\ of\ Different\ Age\ Groups\ Screened}}$$

Table 10 displays the results of this formula for all age groups. Therefore, transition probability for diagnose by breast cancer in each period of our simulation is found separately for each individual in all age groups.

[4] T.C. Sağlık Bakanlığı Numune Eğitim ve Araştırma Hastanesi Onkoloji Kliniği

Table 10: Relative Frequency of Breast Cancer for Age Groups

	40-44	45-49	50-54	55-59	60-64	65-69
Incidence Rate	0.007	0.007	0.007	0.007	0.007	0.007
No of age groups screened	6	6	6	6	6	6
Relative Frequency of Age Group	19.56%	20.05%	19.07%	15.80%	14.46%	11.05%
Incidence Rate of the Age Group	0.82%	0.84%	0.80%	0.66%	0.60%	0.46%

Source: Data Collected fromCancer Early Diagnosis and Treatment Centers

5.3.3 Stage at Diagnosis

The stage of breast cancer at the diagnosis is important for defining the relative mortality rates of the patients. If a breast cancer is diagnosed at early stages, then survival rates can be high. However, if the diagnosis is done at late stages, especially after metastasis, survival rates can be extremely low. Besides from mortality rates, diagnosis stage is also a primary factor in breast cancer treatment options and hence, the money spent on treatment. While, at the early stages of the cancer, main treatment options are chemotherapy, radiotherapy and systematic medical drugs, at late stages heavier medical treatment, mastectomy and surgery may be needed. The delay of the diagnosis of the disease means higher treatment costs. Therefore accurate staging of breast cancer is important both for mammography screened women and for clinically diagnosed women.

5.3.3.1 In Mammography Screened Women

To determine the relative percentages of the breast cancer stages faced in mammography screened women, survey results from Cancer Early Diagnosis and Treatment Centers are used. As explained above, 37,424, 35,866 and 24,639 women were screened in CEDTC's randomly in 2007, 2008 and 2009 successively,

and 222, 195, 166 incidences were reported. Table 11 below displays the stage distribution of these incidences, stage of which can be identified.

Table 11: Breast Cancer Stage Distributions in Screened Women in Detail

	2007	2008	2009	Total
Stage 0	5	11	5	21
Stage I	32	33	27	92
Stage I A				
Stage I B				
Stage II	48	47	37	132
Stage II A	9	15	11	35
Stage II B	11	16	7	34
Stage II C				0
Stage III	13	17	6	36
Stage III A	2	6	7	15
Stage III B			1	1
Stage III C		5	1	6
Stage IV	6	10	9	25
Total	126	165	111	402

Source: Data Collected from Cancer Early Diagnosis and Treatment Centers

For simplicity, these TNM stages are categorized in four main stages in Table 12, and relative average occurrence rate for all stages in 2007 to 2009 are used as the transition probability for entities between diagnose node and stage nodes during the simulation.

Table 12: Breast Cancer Stage Distributions in Screened Women

Stage	Probability
Stage I	28,11%
Stage II	50,00%
Stage III	14,43%
Stage IV	6,22%

Source: Data Collected From Cancer Early Diagnosis and Treatment Centers

5.3.3.2 In Clinically Diagnosed Women

To determine the stage allocations of the diagnosed cases where diagnosis comes out from a clinical symptom, outcomes of the study made by Haydaroğulları et al (Haydaroğlu, et al., 2005) is used with combination of the study by Yılmaz et al. (Yılmaz, et al., 2007) Haydaroğulları et al made a study in Aegean University Hospital, using 3897 breast cancer incidences, half of which are from habitants of Izmir and half of which is coming from out of town, aiming to evaluate these incidences with respect to certain factors. One of the aims of the study was to evaluate relative frequencies of stages at the diagnosis. It is found out that 1,097 of the 3,171 cases are diagnosed at early stages (Stage I and Stage II), 1,923 are diagnosed at Stage III and 151 are diagnosed at the Stage IV. However, separation of early stage cancers into Stage I and Stage II cancers is needed, since different cost parameters are attached to them. The outcomes of the study done by Yılmaz et al are used in this allocation. 17 of the 89 early stage breast cancer incidences in the mentioned study are found to be at Stage I and 72 of 89 are at Stage II. Applying these ratios to the 1,923 cases of early diagnosis (Stage I and Stage II) breast cancer incidences faced in Aegean University Hospital results in 219 Stage I cases and 878 Stage II cases. Therefore relative frequencies of the stages for clinically diagnosed breast cancer, which is used as the transition probabilities between diagnosis node and the stage nodes of the simulation model, are found as given in Table 13.

Table 13: Breast Cancer Stage Distributions in Clinically Diagnosed Women

Stage	Number	Frequency
Stage I	219	6,91%
Stage II	878	27,69%
Stage III	1923	60,64%
Stage IV	151	4,76%
Toplam	3171	100,00%

(Haydaroğlu, et al., 2005), (Yılmaz, et al., 2007)

5.3.4 Cost of Screening

There are basically two cost parameters in the simulation model, cost of screening and cost of treatment, which will be determining factors in chosen strategy. Simulation results will favor the population based screening program if the screening costs are lower with respect to treatment costs and no screening strategies will be favored if the screening costs are high. Therefore, both of these cost values are needed to be estimated carefully.

Cost of mammography screening per woman is taken from the detailed analysis of the cost structures of Cancer Early Diagnosis and Treatment Centers. Results of the surveys conducted in CEDTC's containing the detailed cost analysis are classified into groups as expenditures on goods and services, maintenance expenditures, capital expenditures and personnel expenditures. Economic life years of the medical equipments such as mammography, ultrasound and computers are calculated and yearly amortizations are included in yearly cost of screening. Calculations are not done based on the current capacity usage rates, rather they are done assuming the situation that CEDTC's work at the full capacity due to a projected population based screening program. Moreover calculations are based on the mammography and examination screenings, ultrasound and pathological interventions are discarded. Average screening cost per patient based on mammography and examination screenings are estimated as 15.2 TL in 2007 prices.

Table 14: Screening Cost

Average Screening Cost Per Patient	**15.2 TL**

(Yılmaz, et al., 2007)

Table 15 below illustrates the detailed analysis of the screening costs per patient. The greatest cost item is the personnel expenditures by almost 50 percent of the all expenditures, followed by operating costs and investment costs.

Table 15: Distribution of Screening Costs

Expenditure	Relative Percentage
Personnel	49.1%
Operating Expenditures	33.8%
Investment	14.7%
Maintenance	2.40%
Total	**100%**

(Yılmaz, et al., 2007)

The cost of screening per patient, which is estimated as 15.2 TL, is incurred whenever an entity visits the screening node during simulation. Therefore, at the end of the simulation run, an overall cost of screening is found, with respect to the number of entities visiting the screening node, in other words number of women screened.

5.3.5 Cost of Treatment

The other cost parameter in the simulation model is the cost of treatment. Unlike screening costs, treatment costs are not the same for all breast cancer patients and respect a great variety dependent on some factors, such as age, stage at diagnosis and co morbidity etc. Breast cancer patients diagnosed in old ages are more costly to treat, since there is a greater probability to develop infection or other disease. Similarly, patients with co-morbidity besides the breast cancer also needs special care compared to breast cancer patients only, hence they are more costly to treat. However the most crucial parameter defining the cost of treatment for a

patient is the stage of the cancer at the diagnosis. Studies[5] in literature display the fact that breast cancer treatment costs are very much dependent on the progress of the disease, and other factors are in minor importance. Stage of the disease at the diagnosis is the main parameter in defining treatment cost because the medical intervention method is decided according to the stage. In early stages medical treatment or chemotherapy can be enough the ensure survival, whereas at the later stages heavier and costly treatment options such as mastectomy, or surgery are needed. Therefore in estimating treatment costs, only stage parameter is used and annual treatment cost for each stage that the disease is diagnosed is found.

Treatment and surveillance costs for breast cancer patients are estimated according to the records in registry of Oncology Clinic of Ankara Numune Education and Research Hospital. 35 patients, whose records are kept in detail, diagnosed by breast cancer in different times are chosen randomly. The diagnosis stages of the disease of these 35 chosen patients are as follows; 14 Stage I, 6 Stage II, 9 Stage III and 6 Stage IV. Records of these patients including each type of expenditure in the process of treatment such as medical treatments, radiotherapy, surgery and laboratory tests during 14-57 months were analyzed in detail. The results of the analysis are then adapted to 2007 prices and annual treatment costs per patient with respect to the stage of the breast cancer at the diagnosis is found.

Table 16 presents the average annual treatment costs per patient for each stage that will be charged in each simulation year as long as the patient is in the system. Once an entity comes to one of these stage nodes, corresponding treatment cost is added to the total costs. At the end of the simulation year, if the

[5] (Yılmaz, et al., 2007), (Rojnik, et al., 2008), (Ohnuki, et al., 2006), (Wong, et al., 2007)

entity still remains in the system then these treatment costs are charged again for the next simulation period. These costs are continued to be charged until the entity leaves the system, in other words until the patient dies.

Table 16: Breast Cancer Treatment Costs

Stage	Average Annual Treatment Costs
Stage I	2,580 TL
Stage II	3,624 TL
Stage III	8,735 TL
Stage IV	4,001 TL

(Yılmaz, et al., 2007)

5.3.6 Screening Interval

An 'interval cancer' is a cancer diagnosed between a normal screen, and the time the next screen is due. A screening program with a high percentage of interval cancers is unlikely to make a significant difference to breast cancer mortality. Therefore the choice of screening interval is important to realize higher benefits with lower costs. A long screening interval means enough time for cancerous cells to develop and make progression between two screening intervals. On the other hand, much shorter screening interval may lead to higher rates of false positive results and higher costs of screening with a lower reduction in mortality rates.

A seventeen year study for evaluating the effects of screening interval on the burden of breast cancer carried out by Miltenburg et al in Netherlands, introduced the relative probabilities for patients to develop interval cancer. (Miltenburg, et al., 1998) 14,697 women attending the program are subjected to the mammography screening at different intervals and followed up by seventeen years, and odds ratios for screening intervals are calculated. Table 17 below illustrates the odds ratios to develop interval cancer for each screening interval.

These ratios are multiplied by breast cancer incidence rates for unscreened women to estimate the probability of being diagnosed by breast cancer between two successive screenings. For instance, while the probability of diagnose for an unscreened women aged 50 is 0.80%, given that the result of the first screening is negative the probability of diagnose reduces to 0.43% in successive screenings in a biennial screening strategy.

Table 17: Annual vs. Biennial Screening Odds Ratios

Screening Interval	Odds Ratio
Annual	0.38
Biennial	0.54

(Miltenburg, et al., 1998)

Besides the reduced probability of diagnosis, choice of screening interval has also effects on the stage of the breast cancer at diagnosis. Since there is less time for the progression of the cancerous cells in more frequent screenings, the stage of the disease at the diagnosis is that much lower. White et al made a study to compare the advantages of annual and biennial screening strategies with respect to certain factors. 7,840 patients attending the study were followed-up by five years between 1996 and 2001. 5400 of these patients are subject to annual screenings and 2440 are subject to biennial screenings. The stages of the breast cancers at the diagnosis for those women who had received negative results from previous screenings were derived separately for each screening strategy. Moreover, these results are separated into age groups to see if screening interval has different effects for women in different age groups. The results of the study is presented as percentage of interval cancer stages encountered in annual and biennial screening strategies for all age groups separately in Table 18. According to the results presented, for instance, if a 50 year old woman in annual screening strategy, who had negative mammography result in the previous screening, has

positive result in the current screening than stage of her breast cancer is Stage I with 69%, Stage II with 27% and Stage III with 4% probabilities. These probabilities are used as the transition probabilities between screening and stage nodes for the women who were screened before.

Table 18: Annual vs. Biennial Screening Odds Ratios in Following Screenings

Interval	Annual			Biennial		
Age	<49	50-59	60-69	<49	50-59	60-69
Stage I	67%	69%	74%	62%	66%	76%
Stage II	29%	27%	23%	32%	30%	21%
Stage III	4%	4%	3%	6%	4%	3%

(White, et al., 2004)

5.3.7 False Positive Results

The goal of any screening procedure is to examine a large population of patients and find a small number most likely to have a serious condition. These patients are then referred for further, usually more invasive, testing. Thus a screening exam is not intended to be definitive. It is intended to have a high sensitivity so as to not miss any cancers. The cost of this high sensitivity is a relatively large number of results that would be regarded as suspicious in patients without disease. This is true for mammography. The patients called back for further testing from a screening session are sometimes called as "false positives", implying an error. (http://en.wikipedia.org, 2010)

The study done by Lehman et al with the attendance of 4,091 women to examine the effect of breast density and age on false-positive mammography results introduces that false positive rates of mammography screenings are dependent on the age. (Lehman, et al., 1999) Relative specifities of the mammograms derived during the study; hence the probability of having a false positive result is

summarized in table 19. For instance, if a 50 year old woman who actually does not have breast cancer goes through mammography screening, there is 9.3% probability that she will be diagnosed with breast cancer by mistake.

Table 19: False Positive Ratios for Mammography Screening

Age Group	Mammogram Specificity	False Positive Ratio*
40-49	90.9%	9.2%
50-59	90.7%	9.3%
60-69	91.1%	8.9%

(Lehman, et al., 1999), *False positive/ (True negative + False positive)

These false positive ratios are used as the transition probabilities between "breast cancer negative" node and the "false positive cases" node.

Whenever a patient is diagnosed as breast cancer by mistake, some further operations are needed to realize that she actually has no cancer, in other words she is a false positive case. These further operations have both tangible and intangible costs, which can be named as cost of false positive results. There are both medical costs of these operations and intangible costs due to reduction in the quality of life of the patient. Therefore, these costs should be estimated and included in the simulation for getting more reliable results. Assuming that, among women with an abnormal mammogram, 60.9% required repeat mammography, 27.9% required ultrasound, 4.4% required fine-needle aspiration, and 15.8% required open biopsy. Further treatment costs for false positive results are calculated as 58 TL in 2007 prices. After one-time incurring of this cost, at the end of the year, they are transferred back to the "breast cancer negative" node.

5.3.8 Intangible Costs

It is for sure that breast cancer is a disease that puts a great burden on society in terms of treatment and medicine costs. As stated above, dependent on the stage

that the disease is diagnosed, it incurs costs of lumpectomy, radiation therapy, chemotherapy, mastectomy, surgery as well as the costs of medical substances and salaries of health personnel etc. Besides these tangible and measurable costs there are some other costs, which are hard to measure or estimate. These are intangible costs, including a high variety of costs from the value of time lost in treatment procedure to labor force lost due to the disease. It puts an extra burden on the society when a woman is obliged to participate in treatment process and thus stays away from her usual economic activities. Moreover, some breast cancer treatment procedures such as mastectomy or surgery may cause the patient entirely to lose some part of her body. This is called dismemberment, and may become inappropriate to carry on her usual economic activity.

One method to measure the intangible costs of a disease, combining the mortality rates with the morbidity and figure out an overall summary of disease's burden on the society is calculating quality adjusted life years. A quality adjusted life year (QALY) takes into account both the quantity and quality of life generated by healthcare interventions. It is basically the combination of quantity and quality of life lived. It provides a tool for the assessment of benefits gained from a variety of interventions in terms of health related quality of life and survival for the patient (Philips, 2009).

In calculation of the QALY each health state is weighted by a number from 1 to 0. A year in a perfect health state is valued as 1 and a year less than a perfect health state is valued as less than 1. There are also some debates in literature that there are some health states which are worse than death, thus scale of the QALY should go further below 0. (Sassi, 2006)

The preferred instrument for the measurement and valuation of health related quality of life in NICE (National Institute for Health and Clinical Excellence)

evaluations is the EQ-5D, which measures the health state in 5 dimensions as, mobility, pain or discomfort, self-care, anxiety or depression and usual activities. Some examples about EQ-5D system and corresponding QALY values are presented in table 20 below.

Table 20: EQ-5D QALY Calculation Examples

Health state	Description	Valuation
11111	No problems	1.000
11221	No problems walking about; no problems with self-care; some problems with performing usual activities; some pain or discomfort; not anxious or depressed	0.760
22222	Some problems walking about; some problems washing or dressing self; some problems with performing usual activities; moderate pain or discomfort; moderately anxious or depressed	0.516
12321	No problems walking about; some problems washing or dressing self; unable to perform usual activities; some pain or discomfort; not anxious or depressed	0.329
21123	Some problems walking about; no problems with self-care; no problems with performing usual activities; moderate pain or discomfort; extremely anxious or depressed	0.222
23322	Some problems walking about, unable to wash or dress self, unable to perform usual activities, moderate pain or discomfort, moderately anxious or depressed	0.079
33332	Confined to bed; unable to wash or dress self; unable to perform usual activities; extreme pain or discomfort; moderately anxious or depressed	–0.429

(Philips, 2009)

Quality adjusted life years lost in the time horizon of the disease for breast cancer patients, similar to the other disease, is very much dependent on the treatment procedure carried on. For instance, while medical treatment or chemotherapy may cause little handicaps in five dimensions declared, surgery may cause much more than that. Since the treatment methodology selected is related to the stage of the breast cancer in diagnosis, QALY is also dependent on the diagnosis stage. QALY lost in process is low when the cancer is diagnosed in early stages and can be treated by medical treatment or chemotherapy, however if the diagnosis of the disease falls behind to late stages, QALY lost would be much higher. Especially breast cancer occasions diagnosed after metastasis leads to QALY values close to zero, in other words almost equivalent to death.

There are several studies in literature aiming to calculate QALY lost in the case of breast cancer with respect to the stage that the cancer is diagnosed. These studies endeavor to estimate the QALY by assigning a value for each treatment option reducing the quality of life. Then by attaining these values to patients in randomized clinical trials by grouping them according to the diagnosis stage ends up in the separate QALY values for each stage. Table 21 illustrates the QALY values taken from the literature that is used in our simulation model.

Table 21: QALY Lost According to Stage at Diagnosis

Diagnosis Stage	Stage I	Stage II	Stage III	Stage IV	Death
QALY	0.9	0.8	0.7	0.3	0.0
Lost QALY	0.1	0.2	0.3	0.7	1.0

(Wong, et al., 2007)

During the simulation QALY of the woman for each simulation year is reduced by the lost QALY value corresponding to her diagnosis stage. In the case of a death QALY value is reduced to zero and each year an economical burden due to entirely lost economical activity of the women is incurred.

5.3.8.1 Expressing QALY in Monetary Units

The life quality lost due to the disease can be estimated by QALY methodology for each patient in terms of life years. However since all quantities in our model are expressed in monetary units, QALY should be converted to TL values as well. We need to include increased QALY due to the screening program in monetary units to end up in a total cost-benefit analysis.

Converting QALY to monetary units is quite simple. If how much a woman contributes to the economy can be found, then absence of her economical activity means same amount of burden. Therefore, first thing we need to do is to calculate the contribution of each woman to economy. For calculating this we need gross domestic product and employment data. Dividing gross domestic product (GDP)

to working population results in economic value created per person (working population). Table 22 below shows the GDP values for the last 10 years in 1998 values as well as the employment numbers. Third column in the Table is the division of GDP to the working population; therefore it is the economic contribution of a person to the society. Since all cost values are measured in 2007 values, economic contribution should also be converted to 2007 values. Final column in the Table is the converted values using consumption price index.

Table 22: GDP and GDP per Working Population in 98 prices

Year	GDP (thousand)	Working Population (thousand)	GDP per Working Population (1988 prices)	GDP per Working Population (2007 prices)
2009	97,087,661	**21,277**	4,563	51,334
2008	101,921,730	**21,194**	4,809	54,101
2007	101,254,625	**20,738**	4,883	54,929
2006	96,738,320	**22,330**	4,332	48,737
2005	90,499,731	**22,046**	4,105	46,182
2004	83,485,591	**21,791**	3,831	43,101
2003	76,338,193	**21,147**	3,610	40,611
2002	72,519,831	**21,354**	3,396	38,206
2001	68,309,352	**21,524**	3,174	35,703
2000	72,436,399	**21,581**	3,356	37,761

TUIK

Once economic contributions of working population in past years are found, it can be forecasted for the following 10 years, which is our simulation length. GDP per working population values are forecasted as in Table 23.

Table 23: GDP per Working Capita Estimations

Year	GDP per Working Capita	Year	GDP per Working Capita
2010	55,516	**2015**	67,524
2011	57,733	**2016**	70,221
2012	60,039	**2017**	73,025
2013	62,437	**2018**	75,942
2014	64,931	**2019**	78,975

Author's own calculations

However, incurring these costs for each QALY lost by each woman would be misleading, because a woman getting breast cancer may be unemployed or out of labor force. Therefore we can incur these costs for a fraction of the women that are still working at the time of diagnosis. To determine the correct fraction that this cost to be incurred, labor-force participation and employment rates are needed. The proportion of number of women that are employed in an age group to the overall number of women in that age group indicates how much of these costs will be included. Table 24 below is the employment rate of women in the last 10 years, for all age groups. Using these values the probability of a diagnosed woman, to be in working population can be calculated.

Table 24: Employment Rates of Women

Year	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65+
2009	13,5	25,3	28,8	30,0	30,1	29,0	23,9	20,7	17,4	14,3	5,9
2008	13,9	25,7	28,3	28,0	29,6	26,8	23,3	19,6	16,2	13,0	5,7
2007	13,5	25,1	27,3	27,3	28,2	26,4	22,1	18,9	15,7	13,2	5,8
2006	14,7	24,8	27,5	27,0	29,2	27,9	23,9	21,4	18,3	14,5	6,6

2005	15,0	25,3	26,8	26,2	28,2	27,4	24,9	21,5	18,3	15,2	7,6
2004	16,2	25,8	27,0	26,7	28,9	26,9	24,8	21,8	21,2	17,9	8,7
2003	17,4	25,7	27,9	28,0	29,0	28,0	26,1	23,1	22,9	19,2	10,4
2002	19,6	28,2	28,6	29,5	29,2	28,4	27,8	25,0	22,8	22,5	11,5
2001	19,9	28,6	28,0	29,0	28,9	28,4	26,6	25,8	22,9	19,7	12,4
2000	22,0	27,4	29,3	27,9	28,4	27,6	25,1	24,9	24,2	18,5	11,3

Source: TUIK

The results of the trend analysis are presented in the Table 25 below. These values in Table 25 are the values used in simulation as the probability of a women diagnosed by breast cancer to be actively working. For instance, if a women aged 47 is diagnosed by Stage II breast cancer in 2018, each year by 22.9 percent cost of 14,605 (73,025*0.2) as the value of quality adjusted life years lost due to breast cancer burden will be included, by 87.1 percent no QALY costs will be incurred.

Table 25: Employment Rate Estimations

Year	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65+
2010	12.9	25.1	28.7	30.3	30.3	29.2	23.8	20.3	16.9	13.9	5.59
2011	12.4	24.9	28.7	30.5	30.5	29.3	23.6	19.9	16.3	13.6	5.29
2012	11.8	24.7	28.6	30.8	30.7	29.5	23.5	19.6	15.8	13.2	5.01
2013	11.3	24.4	28.6	31	30.9	29.7	23.4	19.2	15.3	12.9	4.74
2014	10.8	24.2	28.5	31.3	31.1	29.8	23.3	18.8	14.8	12.6	4.49
2015	10.4	24	28.5	31.5	31.3	30	23.1	18.5	14.4	12.3	4.25
2016	9.93	23.8	28.4	31.8	31.5	30.2	23	18.1	13.9	12	4.03

2017	9.5	23.6	28.4	32.1	31.7	30.3	22.9	17.8	13.5	11.7	3.81
2018	9.1	23.4	28.3	32.3	32	30.5	22.8	17.5	13.1	11.4	3.61
2019	8.71	23.2	28.3	32.6	32.2	30.7	22.7	17.1	12.7	11.1	3.42

Author's own calculations

5.3.9 Survival Rates

There are two ways that the entities in the simulation leave the system; either by death caused by breast cancer or death due to another reason. The mortality rates due to other reasons used in the simulations are explained in section 5.3.1. The mortality rates due to other reasons are given as constant probabilities, however mortality rates due to breast cancer needs further analysis. For reliable calculation of the costs and benefits, besides mortality rates, the time horizon between the time of diagnosis and death is also needed. This is necessary to evaluate the time spent on treatment period, and calculate tangible and intangible costs accrued during this period.

The most convenient way encountered in literature for expressing the survival rate for a disease is calculating ratios of the patients that succeeded to survive for a certain time period (usually 5 years) to the all patients. According to the American Cancer Society records, the proportions of the patients in each Stage group who were still alive at the end of fifth year are presented as 5-year survival rates in Table 26.

Table 26: 5-Year Survival Rates

Stage	5-Year Survival Rate
Stage I	100%
Stage II	86%
Stage III	60%
Stage IV	20%

(https://seer.cancer.gov, 2010)

However, this data is not enough to be used in the simulation model for two reasons. First, it is limited with five years, second it gives no information about the mortality probabilities for interval periods. The data required for the simulation should involve mortality probabilities of breast cancer separately for each year for each stage at the diagnosis.

One of the most detailed analyses of breast cancer survival rate in the literature comes from the results of the study done in West Midland, UK. 16,378 breast cancer patients from different diagnose stages are followed up from 1990 to 2004 and relative survival rates of these patients for each year is determined. (www.wmpho.org.uk, 2010) Figure 11 illustrates the results of the study, as the 10-year relative survival rates for breast cancer patients according to stage at diagnosis. As can be seen from the Figure relative survival rates for late-diagnosed breast cancer cases are very low with comparison to early-diagnosed cases.

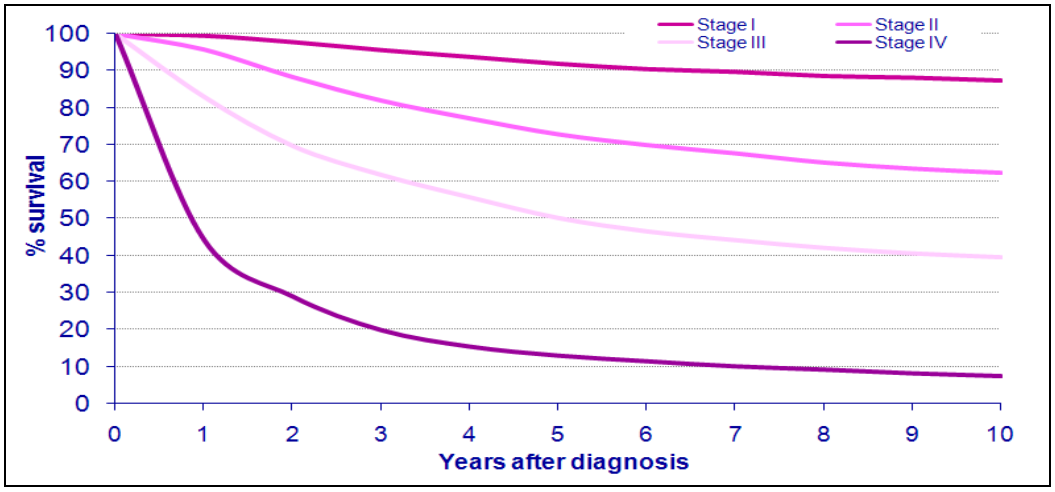

Figure 11: 10 Year Survival Rates (www.wmpho.org.uk, 2010)

These survival rates are calculated as conditional probabilities and should be converted to simple probability rates to be integrated in the simulation model. In

other words, rather than the probability of being alive at the end of the 4th year of diagnosis, the probability to die exactly at the end of 4th year is needed for the model. Table 27 contains the simple probability rates for breast cancer mortality rates calculated using the data in the Figure 11. These values are used as the transition probabilities between stage nodes and "death due to breast cancer" node during simulations.

Table 27: Mortality Probabilities by Stage at Diagnosis

	1	2	3	4	5	6	7	8	9	10
Stage I	0,50	1,72	2,21	1,92	1,99	1,56	0,83	1,25	0,53	0,88
Stage II	4,22	7,74	7,16	5,87	5,54	3,98	3,20	3,68	2,50	1,76
Stage III	16,99	15,97	11,21	9,79	9,99	7,22	5,04	4,74	3,52	2,57
Stage IV	55,72	34,56	31,43	22,42	15,78	11,75	12,01	8,91	10,80	9,30

Author's own calculations

5.3.10 Simulation Length

After all the parameters and variables to be used in the simulation model are set, it is time to decide how many years the simulation will be run to display the cost and benefits of a population based breast cancer screening program accurately. There are some key factors in choosing simulation length. It should be chosen long enough to overcome the possible bias at the beginning of the program and allow the system to approach steady-state values. However, choosing a over-long simulation can cause some shortcomings to occur and system may fail to present the results of the cost benefit analysis accurately. There are many parameters used in simulation model, some of which are forecasted for future using the past data, and some of which are assumed to be constant over time and simply the past average values are used during the simulation. If greater simulation length is used, values of the simulation parameters used in the model may change and fail to reflect the real world. It is possible assumptions and forecast done during

the estimation of model parameters may not hold in the long-run. Moreover, there are also parameters that are hard to estimate for long-run such as survival rates, since there are no such studies done in the literature previously.

Apart from these all, looking at the real-world applications also ensures one to choose a relatively short simulation period. Health sector is a really dynamic sector that treatment methodologies applied are changing rapidly each year parallel to the technological and scientific developments. Therefore, projecting a population based mammography screening program for much longer periods would be inappropriate, since it is highly possible for mammography to be replaced by other new screening methodologies.

Taking all these factors into consideration and taking into account the fact that survival rate data can be reached for 10 years at most, simulation length is chosen as 10 years, which is a long enough period to display the results of a screening program and short enough to overcome the shortcomings.

Table 28: Simulation Length

Simulation Length	10 years

5.4 Results

The simulation model was constructed by the computer software Arena 4.0 and run for 11 scenarios to get the results. Each scenario was run for 20 replications to overcome any bias that could occur. One replication for a scenario took approximately 1.5 minutes; hence it took 7.5 hours in total to get all the results. Those results are then transferred into software Microsoft Excel to derive average values obtained from 20 replications and to construct summarized tables. The detailed results for each scenario containing annual values for each variable obtained are given in Appendix A. Values obtained for each year are discounted to current year to express the total discounted burden of each scenario.

Discounting was made by using 3.5 discount rate, which is the real interest rate for December 2010.

First result obtained from the simulation model is the number of women in the risk group for the following ten years. Given current population and mortality rates data, the female population over 30 years is obtained as in the Table 29. Even these very basic results are enough to put emphasize on the breast cancer screening programs. The results display that society is aging steadily year by year, which means that number of women in the risk group is increasing, since breast cancer is very much dependent on the age. This is a warning about possible increase in the breast cancer incidence rates in the following periods, therefore a greater economic burden unless an action is taken into consideration.

Table 29: Estimated Women Population over 30

Year	Women
2010	10,014
2011	10,282
2012	10,586
2013	10,889
2014	11,191
2015	11,488
2016	11,765
2017	12,035
2018	12,286
2019	12,533

The projected female population is the only result that is same for all the scenarios applied, other results are dependent on the screening strategy used. One of them is the percentage of early diagnosed cases. Table 30 illustrates the early detection ratio obtained for each screening strategy. It is an expected result that as the minimum age to screen or screening interval is increased, early

detection ratio would fall. The results are somewhat supporting this expectation. There is a sharp fall in the early detection ratio with the increased minimum screening age, however the difference between annual and biennial screening policies are not serious that much. For instance, when minimum screening age is increased from 40 to 45 in biennial screening policy early detection ratio is decreased by 22 percent, whereas a shift from biennial screening to annual screening only results in 0.3 percent decrease. Therefore, it is much effective to screen as many female as possible instead of screening the same individual frequently. Another noteworthy result about early detection ratios is that while decreasing minimum screening age results in great increase in early detection ratios for middle aged females, the effect is comparatively less in younger or older females.

Table 30: Early Diagnosis Ratio with respect to Screening Strategy

Strategy	Early (I-II)	Late (III-IV)
No Screening	34.2	65.8
Annual 40+	90.8	9.2
Annual 45+	66.9	33.1
Annual 50+	53.3	46.7
Annual 55+	44.5	55.5
Annual 60+	39.6	60.4
Biennial 40+	91.1	8.9
Biennial 45+	69.0	31.0
Biennial 50+	55.3	44.7
Biennial 55+	45.4	54.6
Biennial 60+	40.6	59.4

Some other results obtained from simulation runs are death and quality adjusted life year losses faced during 10 simulation years. Screening more women and more frequently means earlier diagnosis of the cases, hence less mortality and

QALY loss. Table 31, displaying death and QALY lost numbers, is supporting this statement. While 695 thousand life years will be lost till 2019 if no screening is done, this number would be reduced by 573 thousand by annually screening women aged over 40. Again it is more effective to screen as many females as possible instead of screening same individuals more frequently in terms of death and QALY loss values.

Table 31: Death and QALY Burden by Screening Strategy (thousand)

	Death	QALY Lost	Total
No Screen	324.6	370.7	**695.2**
Annual 40+	59.5	62.4	**121.9**
Annual 45+	91.6	104.4	**196.0**
Annual 50+	128.9	144.2	**273.1**
Annual 55+	155.7	178.2	**333.9**
Annual 60+	173.0	201.3	**374.3**
Biennial 40+	63.9	69.5	**133.4**
Biennial 45+	99.4	110.5	**209.9**
Biennial 50+	127.7	148.1	**275.8**
Biennial 55+	156.6	180.1	**336.6**
Biennial 60+	171.3	202.9	**374.2**

One burden of screening as many people as possible and more frequently is the increased amount of screening costs. Each time an individual is screened it incurs an extra cost which makes screening less favorable. However, there is a greater burden caused by more frequent screening and causes frequent screenings to become less favorable. That is the false positive results due to specificity rates of mammograms. A false positive result is a case resulted from an abnormal mammogram, which indicates that the patient has breast cancer while in fact she has not. There are some further operations mentioned in previous sections to be carried in order to realize that the woman has not breast cancer. Cost of abnormal

mammograms constructs the greatest part of costs due to screening strategies. Table 32 displays the total number of false positive results faced during 10 years simulation. An annual screening strategy has abnormal mammogram numbers twice as the biennial screening strategies, making them less favorable with comparison to biennial strategies.

Table 32: Estimated Number of False Positives

Strategy	Abnormal Mammograms
No Screening	0
Annual 40+	10,341
Annual 45+	7,966
Annual 50+	5,800
Annual 55+	3,869
Annual 60+	2,260
Biennial 40+	5,325
Biennial 45+	4,133
Biennial 50+	3,046
Biennial 55+	2,074
Biennial 60+	1,237

Clearly the most important aspect of the simulation is the costs that are derived from the results of the simulation for each strategy. Costs are representatives of all of the advantages and disadvantages of a screening program in a common unit. Costs are separated into two categories as tangible and intangible costs. Tangible costs are direct costs spent on screening or treatment, whereas intangible costs include the indirect costs resulting from deaths and QALY loss. Table 33 illustrates the discounted tangible costs for each strategy. There are some noteworthy points here. First of all when we compare the annual and biennial screening strategies in terms of screening and treatment costs it is clearly seen that there is almost no difference. A shift from biennial strategy to annual

strategy causes an increase in the screening costs since more women are subjected to screening. However this increase is compensated by decrease in the treatment costs due to earlier detection of breast cancer. However, costs resulting from the false positive cases make the distinction. As more screening means more false positive results and more economic resources wasted, biennial screening is favorable in terms of tangible costs. Second noteworthy point is that tangible costs illustrate a steady decrease with the decrease in the minimum age to screen. Hence, it is effective to screen a**ll** women in the risk group to minimize the tangible burden of breast cancer.

Table 33: Tangible Costs by Screening Strategy (thousand TL)

Strategy	Screening Costs	Treatment Costs	Cost of False Positives	Tangible Costs
No Screening	0	29,844,563	0	29,844,563
Annual 40+	1,419,138	5,239,689	495,466	7,154,293
Annual 45+	1,094,004	8,663,160	381,339	10,138,503
Annual 50+	798,468	11,711,531	277,346	12,787,345
Annual 55+	538,296	14,292,933	184,939	15,016,168
Annual 60+	320,728	16,113,217	107,965	16,541,910
Biennial 40+	745,206	5,880,476	258,375	6,884,056
Biennial 45+	577,744	9,144,036	200,345	9,922,126
Biennial 50+	425,254	12,089,238	147,306	12,661,798
Biennial 55+	291,358	14,420,238	100,192	14,811,788
Biennial 60+	177,763	16,224,469	59,542	16,461,774

Since tangible costs are close to each other, the role of intangible costs becomes crucial in determining optimal screening strategy. Those intangible costs consist of the economic value of life years lost due to breast cancer, either by complete mortality or by morbidity. Unsurprisingly, intangible burden of the breast cancer decreases with increasing screening interval and decreasing minimum screening

age, in terms of both mortality and disability. Earlier the detection of the disease by more frequent screening means less life years lost during treatment process. The reduction in the intangible costs succeeded by screening programs is also in favor of screening as many female as possible to decrease the overall burden of breast cancer. For instance, applying annual screening to those women over 40 results in savings of 10 billion due to continued economical activity. This highlights that intangible benefits are also important for screening programs in reaching optimality.

Table 34: Intangible Costs by Screening Strategy (thousand TL)

Strategy	Cost of Death	Cost of QALY	Intangible Costs
No Screening	17,932,258	15,642,317	33,574,575
Annual 40+	3,385,984	2,922,523	6,308,507
Annual 45+	5,399,497	5,125,397	10,524,894
Annual 50+	7,744,066	6,763,533	14,507,599
Annual 55+	8,615,759	7,849,175	16,464,933
Annual 60+	9,371,508	8,381,450	17,752,958
Biennial 40+	3,364,691	3,262,228	6,396,654
Biennial 45+	5,779,907	5,451,081	10,295,002
Biennial 50+	7,225,223	6,815,978	14,041,201
Biennial 55+	8,665,443	7,711,644	16,377,087
Biennial 60+	9,425,296	8,340,629	17,765,924

When discounted values of all tangible and intangible costs obtained for 10 years time are put together, total burden of each strategy forms as in Table 35. Table displays that the optimal screening strategy for minimizing total costs is screening all women over 40 in every 2 year. Even annual screening has more advantages on decreasing mortality and disability rates, thus decreasing intangible costs, and almost the same tangible costs in terms of screening and treatment, causing much more false positive results makes this strategy

unfavorable to biennial screening. Therefore, all the women over 40 should undergo mammography screening in every two year for effective allocation of resources in struggle with breast cancer.

Table 35: Total Costs by Screening Strategy (thousand TL)

Strategy	Total Costs
No Screening	63,419,138
Annual 40+	13,462,800
Annual 45+	20,663,397
Annual 50+	27,294,944
Annual 55+	31,481,101
Annual 60+	34,294,868
Biennial 40+	13,280,710
Biennial 45+	20,217,128
Biennial 50+	26,702,999
Biennial 55+	31,188,876
Biennial 60+	34,227,698

6 CONCLUSION AND DISCUSSION

Cancer is one of the major health care problems that governments should take care of to reduce the economic and social burden imposed to society. Recently, cancer is the third reason behind the mortality over the whole world by 7.5 million deaths in 2004. The overall mortality numbers are dominated by low income countries where there are greater health problems such as infectious diseases and perinatal conditions. Excluding low income countries makes the cancer caused mortality ratios much drastic for developing and developed world. Cancer is the second reason behind the mortality for developing and developed countries with approximately 20% mortality ratio. Projections for the future mortality rates introduces that burden of the cancer will increase year by year and by 2030 mortality proportion will be increased from 20 to 22 (http://www.who.int, 2010). Apart from the burden on the mortality and decrease in the quality of life, cancer is a disease with great economic burden. By the year 2006 cancer expenditures is estimated as 125 euro per capita and 33 euro per capita for Turkey. Cancer types causing much economical burden and mortality are lung, liver, stomach and colon cancers for males and breast, lung, colon, stomach cancers for females.

Breast cancer is the top cancer in women worldwide and is increasing particularly in developing countries where the majority of cases are diagnosed in later stages. It was recorded that 636,000 incident cases occurred in developed countries and 514,000 in developing countries during 2002. Similar to other countries, breast cancer is by far the mostly occurring cancer type in women in Turkey as well. Breast cancer incidence rate is estimated as 35 in 100,000. This mortality and incidence numbers forces governments to take action against it to increase social welfare.

Unlike other types of cancers breast cancer cannot be attributed to an environmental risk factor causing the development of tumor. For instance, 80 of the lung cancer incidences can be attached to tobacco usage, similarly stomach cancer can be prevented by an appropriate diet. However, there is no such an environmental risk factor causing breast cancer formation, that is controlling the risk factor would mean controlling the cancer. The major risk factor in breast cancer is the age, which is an uncontrollable parameter. Therefore, reducing the burden of breast cancer cannot be done by decreasing incidence rates by controlling risk factors, but it can only be done by early diagnosis of the cases. Early diagnosis of the breast cancer is crucial in choosing treatment strategies, economical resources spent in treatment process and mortality rates. Diagnosing breast cancer in late stages causes higher treatment costs usually with low survival rates.

In struggle with breast cancer governments should look for the effective policies to provide the early diagnosis of the disease. There are two advantages of early diagnosis in economical terms. First the treatment costs will be reduced due to treatment strategies applied to the patient, and second the economical burden due to terminated economical activity of the patients will be less due to reduced mortality and disability. Only way to provide early diagnosis for breast cancer is screening. Screening can be done by mammography, ultrasound or clinical breast examination. Most widely used, cheaper and effective tool for screening is mammography screening. Governments should implement population based mass screening policies to reduce the burden of breast cancer. Most of the EU countries recently have population based breast cancer screening programs. Therefore, such a screening program can be implemented in Turkey to reduce the burden of breast cancer.

A real world simulation model is constructed to test for the economical effectiveness of a population based breast cancer mammography screening program in this thesis. Besides the economical effectiveness of the screening program, most effective screening strategy in terms of screening interval and minimum age to screen is investigated. The databases of World Bank, World Health Organization, International Money Fund, Turkish Institute of Statistics and Turkish Republic Ministry of Health, survey results from Cancer Early Diagnoses and Treatment Centers from different districts of Turkey, namely Antalya, Kayseri, Ankara, Ordu, Denizli, Konya, Bursa, Balıkesir, Sivas, hospital records of Aegen University Hospital and Ankara Numune Hospital and results of the some studies in the literature are used to decide for the optimal screening strategy for Turkey. Optimality is sought in two aspects; one is the tangible economic costs such as screening and treatment costs, and the other is the intangible costs such as the economic values of the life years lost due to breast cancer.

10 years simulation run results indicate that biennial screening of females over 40 is effective in terms of tangible costs and annual screening of females over 40 is effective for intangible considerations. Combining these two aspects and looking for an overall burden of the screening strategies indicates that the optimal strategy for breast cancer screening is to biennially screening women over 40. National program against breast cancer burden prepared by Ministry of Health suggest the biennial screening for females over 50. Therefore this study belies the national policy against breast cancer in terms of minimum screening age. Results of the surveys obtained from Cancer Early Diagnosis and Treatment Centers implies that risk group for breast cancer is not limited with women over 50, and especially in recent years number of breast cancer cases encountered in females

below 50 is quite high. Therefore, results of this thesis suggest the revision of national policy in breast cancer screening to include all women over 40.

Further analysis of the results obtained by the simulation indicates that the biggest handicap of the annual screening policies against biennial screening policies is the higher false positive rates which results in higher false positive costs. A development in technology may lead the mammogram specificities to increase which will end up in lower false positive cases. In such an environment annual screening strategies may prevail over the biennial screening policies and the optimality may change. Therefore optimal screening strategy should be tested each year to see if there is a shift due to environmental factors.

The model constructed here is run for only 10 years due to reasons mentioned in simulation length section. However, results of the simulation indicate that screening more individuals today means trading today's money for future's benefits. 10 year may be insufficient for completely displaying the future benefits and longer simulation runs may result in a change in optimal strategy from biennial to annual. Therefore, if necessary data can be obtained the simulation should be run for longer periods until it reaches steady-state values, and analyze whether there is a shift in the optimal strategy.

Another shortcoming of the study is that the model cannot be run for alternative strategies due to lack of adequate data sources. Optimality of the screening strategies are tested in terms of minimum age to screen, but optimality could not be tested in terms of maximum age to screen. Screening females over a specific age may be economically inefficient due to lower life expectancies and lower conditional incidence probabilities. Results of the simulation are somehow supporting this idea such that, difference in costs between screening strategies for over 60 and over 55 aged females are low with respect to the difference

between screening strategies over 40 and 45 aged females. This points out that screening higher aged women brings less economical benefit with respect to screening lower aged females. Therefore, if adequate data source can be found screening strategies should also be tested for maximum age considerations.

A major issue which is not discussed so far is the practically applicability of the breast cancer screening programs. Theoretically, it is found out that biennially screening all the females in the risk group provides economic efficiency. However, is it possible to screen 20 million individuals in a year? Are there enough resources to apply these strategies? The answers to these questions are probably negative. Resources, in terms of facilities, mammography equipment and physicians recently are insufficient to screen that much individual a year. However, these theoretically optimality may be infeasible in real world. If the optimality is out of the possibility, then the closest point to the optimality in possibility can be used as a proxy to optimality. Screening as many females as possible in the risk group minimizes the economic burden of breast cancer. If the resources are insufficient to screen many individuals, then new investments can be done and number of women included in the screening program can be increased gradually. Moreover, although it is hard to demonstrate in mathematical modeling there are other risk factors that may affect the breast cancer probabilities. Women having those risk factors may have priority in screening since they have higher risk to develop breast cancer. Those risk factors include genetic heritage, age of first birth and menstruation, obesity and diet etc. Mammography screening also can be supported by other screening methodologies to obtain higher efficiency. Those other methodologies include ultrasound, clinical breast examinations and self examinations. Women should be educated on importance of the breast cancer and how to apply self examination, and awareness should be created to provide sustainability.

Finally, supplementary policies should be undertaken to provide the efficiency of the screening program. There should be a force to make all individuals to attend screening program. Efficiency of the screening program should be fenced by laws, legislations, rules and penalties. Women should be obliged to attend screening programs by making laws similar to the ones in Germany and France. In these countries women not attending the screening programs are expelled from the scope of social security for any breast cancer related diseases. Doubtlessly, in order to implement such a strategy and also in order to collect data for further analysis national cancer registry system should be developed.

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Appendix A: Detailed Results of Simulation Runs

A.1 No Screening

		Screen Detected Breast Cancer				Clinically Diagnosed Breast Cancer						
Year	Women Screened	StageI	StageII	StageIII	StageIV	StageI	StageII	StageIII	StageIV	False Positives	Death	QALY Lost
2010	0	0.0	0.0	0.0	0.0	7.4	33.3	77.1	5.9	0	17.9	34.6
2011	0	0.0	0.0	0.0	0.0	10.3	36.2	75.6	6.0	0	29.7	35.1
2012	0	0.0	0.0	0.0	0.0	9.4	33.6	78.1	5.6	0	34.9	35.0
2013	0	0.0	0.0	0.0	0.0	10.5	34.4	79.0	5.9	0	34.8	35.7
2014	0	0.0	0.0	0.0	0.0	9.2	36.2	81.3	6.2	0	43.7	36.8
2015	0	0.0	0.0	0.0	0.0	7.8	36.0	83.1	6.5	0	38.2	37.4
2016	0	0.0	0.0	0.0	0.0	8.3	37.1	85.6	7.6	0	31.6	39.2
2017	0	0.0	0.0	0.0	0.0	10.4	38.1	85.3	7.0	0	37.3	39.1
2018	0	0.0	0.0	0.0	0.0	10.4	39.1	86.6	6.8	0	30.8	39.6
2019	0	0.0	0.0	0.0	0.0	8.6	39.8	82.2	6.7	0	26.0	38.2

Year	Women Screened	Screening Cost	Treatment Cost	Cost of False Positive	Tangible Costs	Cost of Death	Cost of Lost QALY	Intangible Costs	Total Costs
2010	0	0	836,335	0	**836,335**	17.9	281.7	**299.5**	**836,635**
2011	0	0	1,544,308	0	**1,544,308**	47.5	539.4	**586.8**	**1,544,895**
2012	0	0	2,175,188	0	**2,175,188**	82.0	781.5	**863.5**	**2,176,051**
2013	0	0	2,796,546	0	**2,796,546**	116.4	1,028.2	**1,144.6**	**2,797,690**
2014	0	0	3,436,692	0	**3,436,692**	159.6	1,267.9	**1,427.5**	**3,438,119**
2015	0	0	4,017,029	0	**4,017,029**	197.0	1,524.3	**1,721.3**	**4,018,751**
2016	0	0	4,673,491	0	**4,673,491**	227.6	1,815.1	**2,042.7**	**4,675,534**
2017	0	0	5,388,709	0	**5,388,709**	263.6	2,092.4	**2,355.9**	**5,391,064**
2018	0	0	6,082,451	0	**6,082,451**	292.8	2,388.5	**2,681.3**	**6,085,132**
2019	0	0	6,779,406	0	**6,779,406**	316.9	2,688.3	**3,005.1**	**6,782,412**

A.2 Annual Screening Women over 40

		Screen Detected Breast Cancer				Clinically Diagnosed Breast Cancer						
Year	Women Screened	StageI	StageII	StageIII	StageIV	StageI	StageII	StageIII	StageIV	False Positives	Death	QALY Lost
2010	10,014	21.0	37.0	10.9	4.8	0.0	0.0	0.0	0.0	912	6.9	16.1
2011	10,282	18.5	9.9	1.8	0.4	0.0	0.0	0.0	0.0	937	7.7	4.6
2012	10,586	20.1	8.3	2.1	0.3	0.0	0.0	0.0	0.0	988	7.5	4.5
2013	10,889	21.0	10.8	1.8	0.2	0.0	0.0	0.0	0.0	998	6.0	4.9
2014	11,191	23.1	11.4	1.7	0.5	0.0	0.0	0.0	0.0	1,030	6.7	5.4
2015	11,488	22.8	11.7	2.0	0.5	0.0	0.0	0.0	0.0	1,054	6.7	5.5
2016	11,765	24.0	9.9	1.7	0.3	0.0	0.0	0.0	0.0	1,072	4.3	5.1
2017	12,035	24.4	11.4	2.3	0.4	0.0	0.0	0.0	0.0	1,097	6.7	5.6
2018	12,286	21.6	10.4	2.1	0.3	0.0	0.0	0.0	0.0	1,126	3.8	5.0
2019	12,533	26.3	10.5	2.0	0.6	0.0	0.0	0.0	0.0	1,126	3.4	5.7

Year	Women Screened	Screening Cost	Treatment Cost	Cost of False Positive	Tangible Costs	Cost of Death	Cost of Lost QALY	Intangible Costs	Total Costs
2010	10,014	152,213	302,248	52,916	**507,377**	6.9	132.2	**139.1**	**507,516**
2011	10,282	156,292	363,950	54,343	**574,585**	14.5	157.3	**171.8**	**574,757**
2012	10,586	160,900	427,716	57,304	**645,919**	22.0	182.6	**204.6**	**646,124**
2013	10,889	165,511	502,530	57,907	**725,948**	27.9	218.8	**246.7**	**726,195**
2014	11,191	170,105	594,717	59,717	**824,539**	34.6	258.6	**293.1**	**824,833**
2015	11,488	174,612	685,318	61,106	**921,036**	41.1	300.4	**341.5**	**921,378**
2016	11,765	178,832	769,678	62,196	**1,010,706**	45.3	342.0	**387.2**	**1,011,093**
2017	12,035	182,925	874,251	63,652	**1,120,828**	51.8	383.3	**435.0**	**1,121,263**
2018	12,286	186,740	957,881	65,334	**1,209,956**	55.3	424.0	**479.3**	**1,210,435**
2019	12,533	190,504	1,063,965	65,325	**1,319,794**	58.5	473.0	**531.5**	**1,320,326**

A.3 Annual Screening Women Over 45

		Screen Detected Breast Cancer				Clinically Diagnosed Breast Cancer						
Year	Women Screened	StageI	StageII	StageIII	StageIV	StageI	StageII	StageIII	StageIV	False Positives	Death	QALY Lost
2010	7,717	16.3	27.6	9.0	3.6	1.2	4.9	10.9	0.6	697	6.5	17.1
2011	7,908	13.6	6.9	1.3	0.2	1.7	5.9	11.7	0.6	722	10.2	8.4
2012	8,143	15.1	7.6	1.2	0.3	1.2	6.4	13.3	0.9	748	10.8	9.5
2013	8,386	15.0	7.1	2.1	0.2	1.5	6.2	12.8	1.0	770	10.7	9.6
2014	8,612	16.4	7.6	1.4	0.3	1.4	5.9	12.4	1.0	779	11.6	9.4
2015	8,838	16.7	8.5	1.7	0.3	1.9	6.8	12.9	1.1	811	9.3	10.2
2016	9,065	16.2	7.9	2.0	0.2	1.5	5.6	13.3	0.7	825	7.0	9.7
2017	9,283	17.3	7.9	1.2	0.3	2.1	6.5	12.9	1.0	847	10.7	9.9
2018	9,504	16.5	8.8	1.4	0.2	1.6	5.6	13.2	1.0	873	8.0	9.9
2019	9,725	17.8	8.1	1.2	0.5	1.8	5.7	15.3	1.1	894	7.0	10.7

Year	Women Screened	Screening Cost	Treatment Cost	Cost of False Positive	Tangible Costs	Cost of Death	Cost of Lost QALY	Intangible Costs	Total Costs
2010	7,717	117,298	352,743	40,423	**510,464**	6.5	143.5	**149.9**	**510,614**
2011	7,908	120,199	513,017	41,885	**675,101**	16.7	198.7	**215.3**	**675,317**
2012	8,143	123,779	673,894	43,361	**841,034**	27.5	263.2	**290.6**	**841,324**
2013	8,386	127,466	834,096	44,657	**1,006,218**	38.1	328.6	**366.7**	**1,006,585**
2014	8,612	130,896	987,572	45,208	**1,163,676**	49.5	393.2	**442.7**	**1,164,119**
2015	8,838	134,341	1,149,389	47,029	**1,330,759**	58.6	470.8	**529.4**	**1,331,288**
2016	9,065	137,793	1,322,690	47,865	**1,508,347**	65.4	547.4	**612.8**	**1,508,960**
2017	9,283	141,105	1,508,187	49,114	**1,698,406**	75.9	618.7	**694.6**	**1,699,101**
2018	9,504	144,465	1,674,383	50,617	**1,869,464**	83.4	694.5	**777.9**	**1,870,242**
2019	9,725	147,815	1,874,287	51,878	**2,073,980**	90.0	779.0	**869.0**	**2,074,849**

A.4 Annual Screening Women Over 50

		Screen Detected Breast Cancer				Clinically Diagnosed Breast Cancer						
Year	Women Screened	StageI	StageII	StageIII	StageIV	StageI	StageII	StageIII	StageIV	False Positives	Death	QALY Lost
2010	5,489	10.1	18.6	5.1	2.6	2.7	10.6	23.9	1.8	502	7.8	18.8
2011	5,697	10.7	5.2	1.1	0.4	3.0	9.8	23.5	2.0	519	13.9	13.3
2012	5,906	11.4	6.1	1.0	0.4	3.4	10.7	24.7	1.9	536	14.5	14.1
2013	6,106	10.8	5.5	1.0	0.3	2.8	10.1	23.8	1.3	553	16.2	13.0
2014	6,290	11.6	5.0	1.1	0.3	2.9	11.3	24.9	1.7	562	16.0	13.9
2015	6,480	10.9	5.8	1.2	0.3	2.9	11.4	24.3	1.8	589	13.6	13.9
2016	6,669	11.7	5.8	1.3	0.4	2.9	11.0	24.1	2.1	610	13.1	14.1
2017	6,845	11.8	5.3	1.2	0.0	3.2	11.8	22.1	1.7	637	12.7	13.1
2018	7,023	12.4	6.3	1.3	0.4	2.8	12.0	25.5	1.6	637	10.9	14.6
2019	7,195	12.6	6.3	1.2	0.4	3.0	10.9	27.7	2.2	655	10.3	15.4

Year	Women Screened	Screening Cost	Treatment Cost	Cost of False Positive	Tangible Costs	Cost of Death	Cost of Lost QALY	Intangible Costs	Total Costs
2010	5,489	83,433	408,617	29,104	**521,154**	7.8	156.2	**164.0**	**521,318**
2011	5,697	86,591	668,867	30,122	**785,580**	21.6	247.8	**269.4**	**785,849**
2012	5,906	89,777	905,893	31,062	**1,026,731**	36.0	345.5	**381.5**	**1,027,113**
2013	6,106	92,815	1,128,314	32,077	**1,253,206**	52.1	427.7	**479.8**	**1,253,686**
2014	6,290	95,614	1,349,257	32,622	**1,477,493**	68.0	518.4	**586.4**	**1,478,079**
2015	6,480	98,490	1,570,408	34,148	**1,703,045**	81.4	620.7	**702.1**	**1,703,748**
2016	6,669	101,371	1,807,265	35,386	**1,944,022**	94.4	722.6	**817.0**	**1,944,839**
2017	6,845	104,042	2,030,638	36,920	**2,171,601**	106.7	816.6	**923.3**	**2,172,524**
2018	7,023	106,748	2,294,270	36,955	**2,437,972**	117.1	928.1	**1,045.2**	**2,439,018**
2019	7,195	109,362	2,584,904	37,981	**2,732,247**	127.0	1,049.3	**1,176.3**	**2,733,423**

A.5 Annual Screening Women Over 55

		Screen Detected Breast Cancer				Clinically Diagnosed Breast Cancer						
Year	Women Screened	StageI	StageII	StageIII	StageIV	StageI	StageII	StageIII	StageIV	False Positives	Death	QALY Lost
2010	3,642	6.2	11.1	3.3	1.4	3.3	16.0	31.4	2.8	328	9.4	19.6
2011	3,787	6.5	2.9	0.4	0.0	3.6	14.0	33.9	2.7	342	14.7	16.5
2012	3,937	5.7	3.0	0.7	0.1	3.7	14.9	34.1	3.2	350	16.1	17.2
2013	4,091	6.7	3.9	0.6	0.1	3.8	15.0	31.2	2.1	373	17.6	15.8
2014	4,244	7.0	3.2	0.5	0.1	3.5	14.5	33.6	3.2	386	20.1	17.1
2015	4,391	7.9	3.2	1.0	0.2	5.1	14.6	34.0	2.6	397	16.4	17.2
2016	4,520	7.7	3.8	0.8	0.2	4.3	16.9	34.7	3.5	411	14.3	18.5
2017	4,657	8.1	3.5	0.8	0.2	4.1	16.6	37.4	2.5	418	17.8	18.6
2018	4,790	8.2	4.1	1.0	0.2	4.2	15.0	36.2	3.0	424	15.9	18.4
2019	4,930	8.0	3.7	0.9	0.3	4.7	17.3	36.9	3.3	441	13.7	19.3

Year	Women Screened	Screening Cost	Treatment Cost	Cost of False Positive	Tangible Costs	Cost of Death	Cost of Lost QALY	Intangible Costs	Total Costs
2010	3,642	55,358	441,064	19,050	**515,473**	9.4	159.2	**168.6**	**515,641**
2011	3,787	57,555	774,515	19,824	**851,895**	24.1	278.2	**302.3**	**852,197**
2012	3,937	59,849	1,079,820	20,294	**1,159,964**	40.1	398.5	**438.6**	**1,160,402**
2013	4,091	62,183	1,351,854	21,660	**1,435,698**	57.7	503.4	**561.0**	**1,436,259**
2014	4,244	64,510	1,626,964	22,365	**1,713,840**	77.7	613.7	**691.4**	**1,714,531**
2015	4,391	66,737	1,901,842	23,000	**1,991,579**	94.0	737.4	**831.4**	**1,992,410**
2016	4,520	68,709	2,215,623	23,838	**2,308,170**	108.0	877.7	**985.7**	**2,309,156**
2017	4,657	70,780	2,562,315	24,247	**2,657,342**	125.2	1,009.1	**1,134.3**	**2,658,476**
2018	4,790	72,813	2,875,176	24,583	**2,972,571**	140.6	1,140.9	**1,281.5**	**2,973,853**
2019	4,930	74,937	3,213,120	25,558	**3,313,614**	153.8	1,285.8	**1,439.6**	**3,315,054**

A.6 Annual Screening Women Over 60

		Screen Detected Breast Cancer				Clinically Diagnosed Breast Cancer						
Year	Women Screened	StageI	StageII	StageIII	StageIV	StageI	StageII	StageIII	StageIV	False Positives	Death	QALY Lost
2010	2,158	3.3	5.6	2.2	0.6	4.8	15.9	38.7	2.6	191	9.2	19.6
2011	2,249	3.8	1.6	0.5	0.1	4.0	17.3	40.0	3.5	198	18.4	19.2
2012	2,330	4.3	1.5	0.3	0.2	3.4	17.8	40.1	3.5	210	17.1	19.3
2013	2,423	4.1	2.0	0.6	0.1	4.9	17.9	41.7	3.8	214	20.5	20.3
2014	2,515	3.9	2.2	0.6	0.1	5.3	19.6	40.5	2.9	218	24.2	19.6
2015	2,610	3.8	2.4	0.5	0.2	5.2	18.8	41.8	3.4	231	18.7	20.3
2016	2,703	4.2	2.2	0.5	0.2	4.9	18.8	38.7	3.4	238	16.4	19.3
2017	2,795	5.4	2.0	0.7	0.2	5.5	19.0	42.4	3.2	246	19.5	20.5
2018	2,874	4.9	2.5	0.6	0.3	5.3	18.8	44.3	4.5	256	15.4	22.0
2019	2,972	3.9	2.3	0.8	0.1	6.5	19.9	44.6	3.1	258	14.0	21.3

Year	Women Screened	Screening Cost	Treatment Cost	Cost of False Positive	Tangible Costs	Cost of Death	Cost of Lost QALY	Intangible Costs	Total Costs
2010	2,158	32,802	467,932	11,093	**511,826**	9.2	162.0	**171.1**	**511,997**
2011	2,249	34,189	858,425	11,458	**904,072**	27.5	295.6	**323.1**	**904,395**
2012	2,330	35,411	1,178,285	12,154	**1,225,850**	44.6	434.2	**478.8**	**1,226,329**
2013	2,423	36,827	1,539,969	12,427	**1,589,222**	65.0	573.4	**638.4**	**1,589,860**
2014	2,515	38,233	1,868,201	12,656	**1,919,089**	89.0	695.6	**784.6**	**1,919,873**
2015	2,610	39,664	2,176,188	13,386	**2,229,239**	107.5	843.3	**950.7**	**2,230,189**
2016	2,703	41,089	2,493,088	13,827	**2,548,003**	123.4	982.7	**1,106.0**	**2,549,109**
2017	2,795	42,477	2,871,873	14,288	**2,928,639**	142.2	1,128.1	**1,270.3**	**2,929,909**
2018	2,874	43,689	3,247,039	14,836	**3,305,564**	157.0	1,295.6	**1,452.6**	**3,307,016**
2019	2,972	45,170	3,651,737	14,967	**3,711,873**	170.3	1,459.1	**1,629.3**	**3,713,503**

A.7 Biennial Screening Women over 40

		Screen Detected Breast Cancer				Clinically Diagnosed Breast Cancer						
Year	Women Screened	StageI	StageII	StageIII	StageIV	StageI	StageII	StageIII	StageIV	False Positives	Death	QALY Lost
2010	10,014	19.8	40.0	11.0	5.2	0.0	0.0	0.0	0.0	906	6.6	16.9
2011	551	1.9	2.3	0.8	0.3	18.3	8.0	1.0	0.0	53	6.6	4.8
2012	10,037	24.1	12.9	2.6	0.4	0.9	0.4	0.0	0.0	916	7.8	6.2
2013	1,105	2.3	2.8	0.8	0.2	20.2	6.1	0.8	0.0	106	6.1	4.6
2014	10,077	25.7	13.4	2.4	0.3	2.4	0.8	0.2	0.0	911	7.8	6.6
2015	1,676	4.5	2.9	1.2	0.2	18.5	8.1	1.1	0.0	153	7.1	5.3
2016	10,087	25.0	13.9	2.6	0.2	3.1	1.5	0.1	0.0	915	5.2	6.8
2017	2,244	6.0	4.5	0.9	0.5	17.3	7.8	1.1	0.0	207	6.7	5.7
2018	10,046	26.8	12.2	2.4	0.4	4.1	2.1	0.3	0.0	905	5.1	7.0
2019	2,778	7.7	4.9	1.0	0.3	16.7	7.4	0.9	0.0	253	5.0	5.7

Year	Women Screened	Screening Cost	Treatment Cost	Cost of False Positive	Tangible Costs	Cost of Death	Cost of Lost QALY	Intangible Costs	Total Costs
2010	10,014	152,213	312,497	52,565	**517,276**	6.6	140.2	**146.7**	**517,422**
2011	551	8,377	382,108	3,051	**393,535**	13.1	169.5	**182.5**	**393,718**
2012	10,037	152,568	487,354	53,119	**693,041**	20.8	212.7	**233.5**	**693,275**
2013	1,105	16,798	556,508	6,136	**579,442**	26.7	243.2	**269.9**	**579,712**
2014	10,077	153,163	676,731	52,832	**882,726**	34.4	293.0	**327.3**	**883,053**
2015	1,676	25,476	762,350	8,889	**796,714**	41.3	330.3	**371.6**	**797,086**
2016	10,087	153,323	883,546	53,076	**1,089,945**	46.3	386.2	**432.5**	**1,090,377**
2017	2,244	34,105	980,996	11,994	**1,027,095**	52.8	429.0	**481.7**	**1,027,577**
2018	10,046	152,701	1,105,932	52,507	**1,311,141**	57.7	486.4	**544.1**	**1,311,685**
2019	2,778	42,232	1,208,118	14,691	**1,265,041**	62.5	532.9	**595.4**	**1,265,637**

A.8 Biennial Screening Women Over 45

		Screen Detected Breast Cancer				Clinically Diagnosed Breast Cancer						
Year	Women Screened	StageI	StageII	StageIII	StageIV	StageI	StageII	StageIII	StageIV	False Positives	Death	QALY Lost
2010	7,717	15.8	28.1	8.5	3.3	1.5	5.5	12.1	1.0	700	6.6	17.6
2011	459	0.7	1.3	0.6	0.2	13.0	11.5	13.1	1.1	43	10.2	8.9
2012	7,692	18.8	9.0	1.8	0.4	2.1	5.4	12.5	1.2	701	11.6	10.4
2013	935	2.3	2.2	0.6	0.2	14.9	10.7	14.5	0.9	84	10.3	9.6
2014	7,668	21.8	7.6	1.7	0.3	3.4	7.1	13.1	1.3	699	11.0	10.9
2015	1,434	3.6	4.4	0.5	0.3	14.7	12.0	14.9	0.9	131	11.8	10.5
2016	7,623	18.4	9.0	2.1	0.2	4.3	7.3	12.8	1.1	682	9.5	10.8
2017	1,938	6.2	4.3	0.8	0.2	14.8	12.4	13.0	1.0	177	11.2	10.3
2018	7,571	19.3	8.8	1.3	0.3	4.4	6.7	13.4	1.0	688	9.5	10.8
2019	2,442	7.7	4.8	1.1	0.3	15.2	11.1	13.1	1.4	229	7.9	10.9

Year	Women Screened	Screening Cost	Treatment Cost	Cost of False Positive	Tangible Costs	Cost of Death	Cost of Lost QALY	Intangible Costs	Total Costs
2010	7,717	117,298	362,233	40,609	**520,140**	6.6	147.9	**154.5**	**520,295**
2011	459	6,971	528,586	2,506	**538,063**	16.8	205.7	**222.4**	**538,285**
2012	7,692	116,920	702,120	40,646	**859,686**	28.3	276.3	**304.6**	**859,991**
2013	935	14,211	862,887	4,849	**881,947**	38.6	344.6	**383.1**	**882,330**
2014	7,668	116,560	1,056,038	40,542	**1,213,140**	49.5	425.0	**474.5**	**1,213,614**
2015	1,434	21,803	1,237,178	7,598	**1,266,579**	61.2	499.7	**560.8**	**1,267,140**
2016	7,623	115,865	1,415,642	39,547	**1,571,054**	70.4	581.0	**651.3**	**1,571,706**
2017	1,938	29,459	1,593,106	10,266	**1,632,831**	81.4	655.4	**736.8**	**1,633,567**
2018	7,571	115,073	1,779,200	39,910	**1,934,183**	90.6	735.7	**826.3**	**1,935,009**
2019	2,442	37,119	1,963,305	13,268	**2,013,692**	98.3	820.0	**918.3**	**2,014,610**

A.9 Biennial Screening Women Over 50

		Screen Detected Breast Cancer				Clinically Diagnosed Breast Cancer						
Year	Women Screened	StageI	StageII	StageIII	StageIV	StageI	StageII	StageIII	StageIV	False Positives	Death	QALY Lost
2010	5,489	10.9	18.8	6.5	2.5	2.7	11.4	23.6	1.7	496	8.7	19.3
2011	437	1.1	1.4	0.5	0.3	12.6	12.3	24.5	1.7	39	12.5	13.0
2012	5,461	12.2	6.6	0.8	0.2	3.7	11.2	24.0	1.7	489	12.0	13.8
2013	873	2.1	2.4	0.7	0.3	12.8	13.3	23.3	1.5	82	14.6	13.0
2014	5,416	14.2	6.3	0.8	0.4	4.9	11.6	24.3	2.2	491	16.3	14.8
2015	1,311	3.5	2.3	0.6	0.0	11.6	15.1	25.1	2.1	122	14.8	14.1
2016	5,342	12.7	6.5	1.7	0.3	4.5	12.2	25.0	1.9	493	13.0	14.9
2017	1,758	4.5	3.0	0.6	0.2	12.1	13.6	25.7	2.7	160	13.5	14.9
2018	5,265	13.4	6.2	0.6	0.1	5.5	14.7	24.6	2.3	473	11.8	15.2
2019	2,195	5.6	3.3	0.7	0.3	11.7	16.1	25.9	1.8	200	10.8	15.0

Year	Women Screened	Screening Cost	Treatment Cost	Cost of False Positive	Tangible Costs	Cost of Death	Cost of Lost QALY	Intangible Costs	Total Costs
2010	5,489	83,433	423,314	28,788	**535,535**	8.7	158.3	**167.0**	**535,702**
2011	437	6,643	676,072	2,265	**684,980**	21.2	249.1	**270.3**	**685,250**
2012	5,461	83,009	917,508	28,377	**1,028,893**	33.1	352.5	**385.5**	**1,029,278**
2013	873	13,263	1,150,898	4,771	**1,168,931**	47.5	438.9	**486.4**	**1,169,418**
2014	5,416	82,327	1,399,153	28,501	**1,509,981**	63.7	541.2	**604.9**	**1,510,586**
2015	1,311	19,926	1,621,442	7,059	**1,648,427**	78.3	639.4	**717.7**	**1,649,144**
2016	5,342	81,200	1,869,596	28,617	**1,979,413**	90.9	749.6	**840.5**	**1,980,253**
2017	1,758	26,716	2,125,889	9,271	**2,161,876**	103.9	859.1	**962.9**	**2,162,839**
2018	5,265	80,035	2,385,350	27,428	**2,492,813**	115.3	971.8	**1,087.1**	**2,493,900**
2019	2,195	33,365	2,662,407	11,606	**2,707,377**	125.8	1,088.7	**1,214.4**	**2,708,592**

A.10 Biennial Screening Women Over 55

		Screen Detected Breast Cancer				Clinically Diagnosed Breast Cancer						
Year	Women Screened	StageI	StageII	StageIII	StageIV	StageI	StageII	StageIII	StageIV	False Positives	Death	QALY Lost
2010	3,642	5.9	10.2	3.4	1.3	3.7	14.6	32.7	2.4	326	9.4	19.3
2011	367	0.7	1.5	0.4	0.2	9.0	16.5	32.6	3.0	33	16.6	16.6
2012	3,583	7.8	3.3	0.6	0.5	3.8	15.6	34.7	3.3	331	16.4	18.1
2013	748	1.8	1.5	0.3	0.2	9.9	17.0	32.2	2.2	71	16.3	16.2
2014	3,498	7.9	3.8	0.7	0.3	5.5	15.4	34.8	2.6	311	21.2	17.8
2015	1,128	1.8	2.1	0.6	0.3	10.1	15.6	34.9	2.8	104	17.2	17.5
2016	3,412	6.8	4.4	0.6	0.1	5.8	17.3	34.8	3.0	304	15.5	18.3
2017	1,493	4.4	2.2	0.5	0.4	9.3	17.3	35.8	3.1	136	16.9	18.5
2018	3,341	7.1	3.3	0.7	0.4	7.1	17.5	37.0	3.4	298	15.2	19.5
2019	1,825	4.3	2.7	0.5	0.1	9.9	17.2	36.0	2.6	159	12.1	18.2

Year	Women Screened	Screening Cost	Treatment Cost	Cost of False Positive	Tangible Costs	Cost of Death	Cost of Lost QALY	Intangible Costs	Total Costs
2010	3,642	55,358	443,707	18,914	**517,979**	9.4	157.4	**166.8**	**518,146**
2011	367	5,584	767,095	1,929	**774,607**	26.0	269.6	**295.6**	**774,902**
2012	3,583	54,456	1,069,235	19,210	**1,142,901**	42.2	401.1	**443.3**	**1,143,345**
2013	748	11,367	1,351,351	4,115	**1,366,833**	58.5	512.7	**571.2**	**1,367,404**
2014	3,498	53,167	1,667,715	18,044	**1,738,925**	79.5	629.0	**708.5**	**1,739,634**
2015	1,128	17,146	1,941,677	6,058	**1,964,881**	96.5	752.1	**848.6**	**1,965,730**
2016	3,412	51,860	2,248,339	17,638	**2,317,837**	111.7	885.9	**997.6**	**2,318,835**
2017	1,493	22,694	2,570,964	7,885	**2,601,542**	128.1	1,021.9	**1,150.0**	**2,602,692**
2018	3,341	50,782	2,910,736	17,293	**2,978,810**	142.9	1,167.0	**1,309.8**	**2,980,120**
2019	1,825	27,745	3,236,497	9,234	**3,273,475**	154.5	1,308.5	**1,463.0**	**3,274,938**

A.11 Biennial Screening Women Over 60

		Screen Detected Breast Cancer				Clinically Diagnosed Breast Cancer						
Year	Women Screened	StageI	StageII	StageIII	StageIV	StageI	StageII	StageIII	StageIV	False Positives	Death	QALY Lost
2010	2,158	3.2	5.9	2.0	0.7	5.5	16.9	38.8	2.9	187	9.3	20.1
2011	291	0.6	0.6	0.3	0.1	7.2	19.9	40.3	2.9	24	18.1	19.1
2012	2,049	4.3	2.2	0.5	0.1	5.1	17.7	39.3	3.5	185	19.5	19.3
2013	589	1.3	1.7	0.3	0.2	8.1	17.8	39.7	2.9	49	19.6	19.0
2014	1,961	3.7	2.2	0.4	0.1	5.5	19.1	39.7	2.8	170	22.3	19.2
2015	865	1.6	1.1	0.1	0.1	7.5	19.4	40.3	3.2	77	18.4	19.4
2016	1,893	3.6	1.9	0.4	0.1	6.5	19.3	46.5	3.4	168	17.0	21.7
2017	1,109	2.7	2.3	0.5	0.2	7.8	20.7	43.4	4.3	97	18.2	21.9
2018	1,864	3.1	2.0	0.5	0.2	6.5	22.1	43.3	3.6	166	16.1	21.5
2019	1,304	3.5	1.7	0.3	0.3	8.1	21.9	44.1	3.4	114	12.9	21.8

Year	Women Screened	Screening Cost	Treatment Cost	Cost of False Positive	Tangible Costs	Cost of Death	Cost of Lost QALY	Intangible Costs	Total Costs
2010	2,158	32,802	474,281	10,872	**517,955**	9.3	164.9	**174.2**	**518,129**
2011	291	4,429	866,426	1,380	**872,235**	27.4	299.5	**326.9**	**872,562**
2012	2,049	31,139	1,191,646	10,747	**1,233,532**	46.8	431.7	**478.4**	**1,234,010**
2013	589	8,958	1,514,867	2,854	**1,526,679**	66.3	559.6	**625.9**	**1,527,304**
2014	1,961	29,806	1,841,676	9,837	**1,881,319**	88.6	686.4	**774.9**	**1,882,094**
2015	865	13,141	2,141,675	4,449	**2,159,265**	106.8	827.8	**934.5**	**2,160,200**
2016	1,893	28,769	2,537,414	9,715	**2,575,898**	123.5	991.7	**1,115.2**	**2,577,013**
2017	1,109	16,863	2,922,719	5,635	**2,945,217**	141.4	1,154.7	**1,296.1**	**2,946,513**
2018	1,864	28,338	3,306,769	9,645	**3,344,752**	157.1	1,314.5	**1,471.6**	**3,346,224**
2019	1,304	19,816	3,709,011	6,595	**3,735,421**	169.5	1,486.9	**1,656.3**	**3,737,078**

APPENDIX B: SIMAN CODE OF THE SIMULATION MODEL

B.1 Blocks

```
Age20_24        CREATE,       3075::NEXT(0$);
0$              ASSIGN:       agegroup=1;
main            BRANCH,       1:
                  If,(PrevScreened==1)*(BiennialStrategy==1)*(year-
lastscreen<=1),bien,Yes:
                  If,agegroup<=4,under30,Yes:
                  If,(agegroup>=lowestage)*(agegroup<=10),screening,Yes:
                  If,agegroup>=11,end,Yes:
                  Else,unscreened,Yes;
bien            BRANCH,       1:
with,0.042*RelativeFreq(agegroup)*(PrevUnscreened+PrevScreened*0.38),Positiv
e2,Yes:
                  Else,Negative2,Yes;
Positive2       COUNT:        600+year,1;
29$             BRANCH,       1:
With,0.0691*PrevUnscreened+PrevScreened*ASSP(1,agegroup),StageI2,Yes:
With,0.2769*PrevUnscreened+PrevScreened*ASSP(2,agegroup),StageII2,Yes:
With,0.6064*PrevUnscreened+PrevScreened*ASSP(3,agegroup),StageIII2,Yes:
With,0.0476*PrevUnscreened+PrevScreened*ASSP(4,agegroup),StageIV2,Yes;
StageI2         COUNT:        1400+year,1;
21$             ASSIGN:       stage=1;
treat           COUNT:        400+year,TreatmentCost(stage);
25$             BRANCH,       1:
                  With,SurvivalRate(year,stage),death,Yes:
                  Else,qalyburden,Yes;
death           COUNT:        300+year,1;
deathburden     COUNT:        1800+year,1;
28$             COUNT:
2000+year,DISC(LFPR(agegroup,year),GDP(year),1,0);
26$             WAIT:         365;
33$             BRANCH,       1:
                  If,agegroup==12,wouldeath,Yes:
                  Else,ageincrease3,Yes;
wouldeath       BRANCH,       1:
                  With,deathrate(agegroup),end,Yes:
```

```
                  Else,deathburden,Yes;
end               DISPOSE:      No;

ageincrease3   ASSIGN:
agegroup=DISC(0.8,agegroup,1,agegroup+1):NEXT(wouldddeath);
qalyburden     ASSIGN:
qaly=(stage==1)*0.1+(stage==2)*0.2+(stage==3)*0.3+(stage==4)*0.7;
izle2             COUNT:       1900+year,qaly*10;
izle              COUNT:
2100+year,QALY*(DISC(LFPR(agegroup,year),GDP(year),1,0));
27$               WAIT:        365;
36$               BRANCH,      1:
                  With,deathrate(agegroup),end,Yes:
                  Else,olmeyen,Yes;
olmeyen           BRANCH,      1:
                  If,agegroup==12,treat,Yes:
                  Else,ageincrease2,Yes;
ageincrease2   ASSIGN:
agegroup=DISC(0.8,agegroup,1,agegroup+1):NEXT(treat);
StageII2          COUNT:       1500+year,1;
22$               ASSIGN:      stage=2:NEXT(treat);
StageIII2         COUNT:       1600+year,1;
23$               ASSIGN:      stage=3:NEXT(treat);
StageIV2          COUNT:       1700+year,1;
24$               ASSIGN:      stage=4:NEXT(treat);
Negative2         BRANCH,      1:
                  With,deathrate(agegroup),end,Yes:
                  Else,nextyear,Yes;
nextyear          WAIT:        365;
32$               BRANCH,      1:
                  If,agegroup==12,main,Yes:
                  Else,ageincrease1,Yes;
ageincrease1   ASSIGN:
agegroup=DISC(0.8,agegroup,1,agegroup+1):NEXT(main);
under30           WAIT:        365:NEXT(ageincrease1);
Screening         COUNT:       100+year,1;
35$               ASSIGN:      lastscreen=year;
16$               BRANCH,      1:
                  With,
0.042*RelativeFreq(agegroup)*(PrevUnscreened+PrevScreened*(AnnualStrategy*
0.38+BiennialStrategy*0.54)),
                  Positive,Yes:
```

```
                  Else,Negative,Yes;
Positive          COUNT:
((800+year)*PrevUnscreened)+((700+year)*PrevScreened),1;
30$               BRANCH,      1:
                  With,

PrevUnscreened*FSSP(1)+PrevScreened*AnnualStrategy*ASSP(1,agegroup)+Prev
Screened*BiennialStrategy*BSSP(1,agegroup),
                  StageI,Yes:
                  With,
PrevUnscreened*FSSP(2)+PrevScreened*AnnualStrategy*ASSP(2,agegroup)+Prev
Screened*BiennialStrategy*BSSP(2,agegroup),
                  StageII,Yes:
                  With,
PrevUnscreened*FSSP(3)+PrevScreened*AnnualStrategy*ASSP(3,agegroup)+Prev
Screened*BiennialStrategy*BSSP(3,agegroup),
                  StageIII,Yes:
                  With,
PrevUnscreened*FSSP(4)+PrevScreened*AnnualStrategy*ASSP(4,agegroup)+Prev
Screened*BiennialStrategy*BSSP(4,agegroup),
                  StageIV,Yes;
StageI            COUNT:       1000+year,1;
17$               ASSIGN:      stage=1:NEXT(treat);
StageII           COUNT:       1100+year,1;
18$               ASSIGN:      stage=2:NEXT(treat);
StageIII          COUNT:       1200+year,1;
19$               ASSIGN:      stage=3:NEXT(treat);
StageIV           COUNT:       1300+year,1;
20$               ASSIGN:      stage=4:NEXT(treat);
Negative          BRANCH,      1:
                  With,FalsePositive(agegroup),FalsePositives,Yes:
                  Else,TrueNegative,Yes;
FalsePositives    COUNT:       500+year,1;
31$               COUNT:       2300+year,58;
34$               ASSIGN:      PrevScreened=1:
                  PrevUnscreened=0:NEXT(Negative2);
TrueNegative      ASSIGN:      PrevScreened=1:
                  PrevUnscreened=0:NEXT(Negative2);
unscreened        COUNT:       200+year,1:NEXT(bien);
Age25_29          CREATE,      3202::NEXT(1$);
1$                ASSIGN:      agegroup=2:NEXT(main);
Age30_34          CREATE,      2913::NEXT(2$);
```

```
2$              ASSIGN:     agegroup=3:NEXT(main);
Age35_39        CREATE,     2740::NEXT(3$);
3$              ASSIGN:     agegroup=4:NEXT(main);
Age40_44        CREATE,     2297::NEXT(4$);
4$              ASSIGN:     agegroup=5:NEXT(main);
Age45_49        CREATE,     2228::NEXT(5$);
5$              ASSIGN:     agegroup=6:NEXT(main);


Age50_54        CREATE,     1847::NEXT(6$);
6$              ASSIGN:     agegroup=7:NEXT(main);
Age55_59        CREATE,     1484::NEXT(7$);
7$              ASSIGN:     agegroup=8:NEXT(main);
Age60_64        CREATE,     1237::NEXT(8$);
8$              ASSIGN:     agegroup=9:NEXT(main);
Age65_69        CREATE,     921::NEXT(9$);
9$              ASSIGN:     agegroup=10:NEXT(main);
Age70_74        CREATE,     737::NEXT(10$);
10$             ASSIGN:     agegroup=11:NEXT(main);
Age75over       CREATE,     1203::NEXT(11$);
11$             ASSIGN:     agegroup=12:NEXT(main);
12$             CREATE,     1:1,9:NEXT(13$);
13$             ASSIGN:     year=year+1;
15$             SIGNAL:     365;
14$             DISPOSE:    No;
```

B.2 Variables

```
PROJECT,    "Unnamed Project","Engin",,,No,Yes,Yes,Yes,No,No,Yes;

ATTRIBUTES:  lastscreen:
        PrevUnscreened,1:
        agegroup:
        qaly:
        stage,0:
        PrevScreened,0:
        FP,0;

VARIABLES:   1,LostQALY1,CLEAR(System):
        2,LostQALY2,CLEAR(System):
        3,LostQALY3,CLEAR(System):
```

4,LostQALY4,CLEAR(System):
5,LostQALY5,CLEAR(System):
6,LostQALY6,CLEAR(System):
7,LostQALY7,CLEAR(System):
8,LostQALY8,CLEAR(System):
9,LostQALY9,CLEAR(System):
10,LostQALY10,CLEAR(System):
FSSP(4),CLEAR(System),0.281,0.5,0.1443,0.0622:
lowestage,CLEAR(System),9:

deathrate(14),CLEAR(System),0.0002,0.0002,0.0003,0.0004,0.0006,0.0010,0.0017,0.0028,0.0048,0.0084,0.0155,0.0415,
0.0415,0.0415:
AnnualStrategy,CLEAR(System),0:
FalsePositive(12),CLEAR(System),0,0,0.073,0.073,0.092,0.092,0.093,0.093,0.089,0.089,0.081,0.081:
LFPR(14,10),CLEAR(System),0,0,0.303,0.303,0.292,0.238,0.203,0.169,0.139,0.0559,0.0559,0.0559,0.0559,0.0559,0,0,
0.305,0.305,0.293,0.236,0.199,0.163,0.136,0.0529,0.0529,0.0529,0.0529,0.0529,0,0,0.308,0.307,0.295,0.235,0.196,
0.158,0.132,0.0501,0.0501,0.0501,0.0501,0.0501,0,0,0.31,0.309,0.297,0.234,0.192,0.153,0.129,0.0474,0.0474,0.0474,
0.0474,0.0474,0,0,0.313,0.311,0.298,0.233,0.188,0.148,0.126,0.0449,0.0449,0.0449,0.0449,0.0449,0,0,0.315,0.313,0.3,
0.231,0.185,0.144,0.123,0.0425,0.0425,0.0425,0.0425,0.0425,0,0,0.318,0.315,0.302,0.23,0.181,0.139,0.12,0.0403,
0.0403,0.0403,0.0403,0.0403,0,0,0.321,0.317,0.303,0.229,0.178,0.135,0.117,0.0381,0.0381,0.0381,0.0381,0.0381,0,0,
0.323,0.32,0.305,0.228,0.175,0.131,0.114,0.0361,0.0361,0.0361,0.0361,0.0361,0,0,0.326,0.322,0.307,0.227,0.171, 0.127,0.111,0.0342,0.0342,0.0342,0.0342,0.0342:
GDP(10),CLEAR(System),55516,57733,60039,62437,64931,67524,70221,73025,75942,78975:
BiennialStrategy,CLEAR(System),1:
SurvivalRate(10,4),CLEAR(System),0.005,0.0172,0.0221,0.0192,0.0199,0.0156,0.0083,0.0125,0.0053,0.0088,0.0422,
0.0774,0.0716,0.0587,0.0554,0.0398,0.032,0.0368,0.025,0.0176,0.1699,0.1597,0.1121,0.0979,0.0999,0.0722,0.0504,
0.0474,0.0352,0.0257,0.5572,0.3456,0.3143,0.2242,0.1578,0.1175,0.1201,0.0891,0.108,0.093:
year,CLEAR(System),1:
TreatmentCost(4),CLEAR(System),2580,3624,8735,4001:

RelativeFreq(14),CLEAR(System),0,0,0,0,0.1956,0.2005,0.1907,0.1580,0.1446,0.1105,
0,0,0,0:
ASSP(4,14),CLEAR(System),0,0,0,0,0,0,0,0,0.67,0.29,0.04,0,0.67,0.29,0.04,0,0.67,0.29
,0.04,0,0.67,0.29,0.04,0,0.69,
0.27,0.04,0,0.69,0.27,0.04,0,0.74,0.23,0.03,0,0.74,0.23,0.03,0,0.78,0.19,0.03,0,0.78,0.19,
0.03,0,0.78,0.19,0.03,0,
0.78,0.19,0.03,0:
BSSP(4,14),CLEAR(System),0,0,0,0,0,0,0,0,0.62,0.32,0.06,0,0.62,0.32,0.06,0,0.62,0.32,
0.06,0,0.62,0.32,0.06,0,0.66,
0.30,0.04,0,0.66,0.30,0.04,0,0.76,0.21,0.03,0,0.76,0.21,0.03,0,0.76,0.21,0.03,0,0.76,0.21,
0.03,0,0.76,0.21,0.03,0,
0.76,0.21,0.03,0;

COUNTERS: 101,Screened1,,Replicate:
102,Screened2,,Replicate:
103,Screened3,,Replicate:
104,Screened4,,Replicate:
105,Screened5,,Replicate:
106,Screened6,,Replicate:
107,Screened7,,Replicate:
108,Screened8,,Replicate:
109,Screened9,,Replicate:
110,Screened10,,Replicate:
201,Unscreened1,,Replicate:
202,Unscreened2,,Replicate:
203,Unscreened3,,Replicate:
204,Unscreened4,,Replicate:
205,Unscreened5,,Replicate:
206,Unscreened6,,Replicate:
207,Unscreened7,,Replicate:
208,Unscreened8,,Replicate:
209,Unscreened9,,Replicate:
210,Unscreened10,,Replicate:
301,DeathCancer1,,Replicate:
302,DeathCancer2,,Replicate:
303,DeathCancer3,,Replicate:
304,DeathCancer4,,Replicate:
305,DeathCancer5,,Replicate:
306,DeathCancer6,,Replicate:
307,DeathCancer7,,Replicate:
308,DeathCancer8,,Replicate:
309,DeathCancer9,,Replicate:

310,DeathCancer10,,Replicate:
401,TreatmentCosts1,,Replicate:
402,TreatmentCosts2,,Replicate:
403,TreatmentCosts3,,Replicate:
404,TreatmentCosts4,,Replicate:
405,TreatmentCosts5,,Replicate:
406,TreatmentCosts6,,Replicate:
407,TreatmentCosts7,,Replicate:
408,TreatmentCosts8,,Replicate:
409,TreatmentCosts9,,Replicate:
410,TreatmentCosts10,,Replicate:
501,FalsePositives1,,Replicate:
502,FalsePositives2,,Replicate:
503,FalsePositives3,,Replicate:
504,FalsePositives4,,Replicate:
505,FalsePositives5,,Replicate:
506,FalsePositives6,,Replicate:
507,FalsePositives7,,Replicate:
508,FalsePositives8,,Replicate:
509,FalsePositives9,,Replicate:
510,FalsePositives10,,Replicate:
701,DiaagnosedInLater1,,Replicate:
702,DiaagnosedInLater2,,Replicate:
703,DiaagnosedInLater3,,Replicate:
704,DiaagnosedInLater4,,Replicate:
705,DiaagnosedInLater5,,Replicate:
706,DiaagnosedInLater6,,Replicate:
707,DiaagnosedInLater7,,Replicate:
708,DiaagnosedInLater8,,Replicate:
709,DiaagnosedInLater9,,Replicate:
710,DiaagnosedInLater10,,Replicate:
801,DiaagnosedInFirst1,,Replicate:
802,DiaagnosedInFirst2,,Replicate:
803,DiaagnosedInFirst3,,Replicate:
804,DiaagnosedInFirst4,,Replicate:
805,DiaagnosedInFirst5,,Replicate:
806,DiaagnosedInFirst6,,Replicate:
807,DiaagnosedInFirst7,,Replicate:
808,DiaagnosedInFirst8,,Replicate:
809,DiaagnosedInFirst9,,Replicate:
810,DiaagnosedInFirst10,,Replicate:
901,Screening Cost,,Replicate:

1001,ScreenedStageI1,,Replicate:
1002,ScreenedStageI2,,Replicate:
1003,ScreenedStageI3,,Replicate:
1004,ScreenedStageI4,,Replicate:
1005,ScreenedStageI5,,Replicate:
1006,ScreenedStageI6,,Replicate:
1007,ScreenedStageI7,,Replicate:
1008,ScreenedStageI8,,Replicate:
1009,ScreenedStageI9,,Replicate:
1010,ScreenedStageI10,,Replicate:
1101,ScreenedStageII1,,Replicate:
1102,ScreenedStageII2,,Replicate:
1103,ScreenedStageII3,,Replicate:
1104,ScreenedStageII4,,Replicate:
1105,ScreenedStageII5,,Replicate:
1106,ScreenedStageII6,,Replicate:
1107,ScreenedStageII7,,Replicate:
1108,ScreenedStageII8,,Replicate:
1109,ScreenedStageII9,,Replicate:
1110,ScreenedStageII10,,Replicate:
1201,ScreenedStageIII1,,Replicate:
1202,ScreenedStageIII2,,Replicate:
1203,ScreenedStageIII3,,Replicate:
1204,ScreenedStageIII4,,Replicate:
1205,ScreenedStageIII5,,Replicate:
1206,ScreenedStageIII6,,Replicate:
1207,ScreenedStageIII7,,Replicate:
1208,ScreenedStageIII8,,Replicate:
1209,ScreenedStageIII9,,Replicate:
1210,ScreenedStageIII10,,Replicate:
1301,ScreenedStageIV1,,Replicate:
1302,ScreenedStageIV2,,Replicate:
1303,ScreenedStageIV3,,Replicate:
1304,ScreenedStageIV4,,Replicate:
1305,ScreenedStageIV5,,Replicate:
1306,ScreenedStageIV6,,Replicate:
1307,ScreenedStageIV7,,Replicate:
1308,ScreenedStageIV8,,Replicate:
1309,ScreenedStageIV9,,Replicate:
1310,ScreenedStageIV10,,Replicate:
1401,ClincalStageI1,,Replicate:
1402,ClincalStageI2,,Replicate:

1403,ClincalStageI3,,Replicate:
1404,ClincalStageI4,,Replicate:
1405,ClincalStageI5,,Replicate:
1406,ClincalStageI6,,Replicate:
1407,ClincalStageI7,,Replicate:
1408,ClincalStageI8,,Replicate:
1409,ClincalStageI9,,Replicate:
1410,ClincalStageI10,,Replicate:
1501,ClincalStageII1,,Replicate:
1502,ClincalStageII2,,Replicate:
1503,ClincalStageII3,,Replicate:
1504,ClincalStageII4,,Replicate:
1505,ClincalStageII5,,Replicate:
1506,ClincalStageII6,,Replicate:
1507,ClincalStageII7,,Replicate:
1508,ClincalStageII8,,Replicate:
1509,ClincalStageII9,,Replicate:
1510,ClincalStageII10,,Replicate:
1601,ClincalStageIII1,,Replicate:
1602,ClincalStageIII2,,Replicate:
1603,ClincalStageIII3,,Replicate:
1604,ClincalStageIII4,,Replicate:
1605,ClincalStageIII5,,Replicate:
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1608,ClincalStageIII8,,Replicate:
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1610,ClincalStageIII10,,Replicate:
1701,ClinicalStageIV1,,Replicate:
1702,ClinicalStageIV2,,Replicate:
1703,ClinicalStageIV3,,Replicate:
1704,ClinicalStageIV4,,Replicate:
1705,ClinicalStageIV5,,Replicate:
1706,ClinicalStageIV6,,Replicate:
1707,ClinicalStageIV7,,Replicate:
1708,ClinicalStageIV8,,Replicate:
1709,ClinicalStageIV9,,Replicate:
1710,ClinicalStageIV10,,Replicate:
1801,BurdDeath1,,Replicate:
1802,BurdDeath2,,Replicate:
1803,BurdDeath3,,Replicate:
1804,BurdDeath4,,Replicate:

1805,BurdDeath5,,Replicate:
1806,BurdDeath6,,Replicate:
1807,BurdDeath7,,Replicate:
1808,BurdDeath8,,Replicate:
1809,BurdDeath9,,Replicate:
1810,BurdDeath10,,Replicate:
1901,BurdQALY1,,Replicate:
1902,BurdQALY2,,Replicate:
1903,BurdQALY3,,Replicate:
1904,BurdQALY4,,Replicate:
1905,BurdQALY5,,Replicate:
1906,BurdQALY6,,Replicate:
1907,BurdQALY7,,Replicate:
1908,BurdQALY8,,Replicate:
1909,BurdQALY9,,Replicate:
1910,BurdQALY10,,Replicate:
2001,EcBurdDeath1,,Replicate:
2002,EcBurdDeath2,,Replicate:
2003,EcBurdDeath3,,Replicate:
2004,EcBurdDeath4,,Replicate:
2005,EcBurdDeath5,,Replicate:
2006,EcBurdDeath6,,Replicate:
2007,EcBurdDeath7,,Replicate:
2008,EcBurdDeath8,,Replicate:
2009,EcBurdDeath9,,Replicate:
2010,EcBurdDeath10,,Replicate:
2101,EcBurdQALY1,,Replicate:
2102,EcBurdQALY2,,Replicate:
2103,EcBurdQALY3,,Replicate:
2104,EcBurdQALY4,,Replicate:
2105,EcBurdQALY5,,Replicate:
2106,EcBurdQALY6,,Replicate:
2107,EcBurdQALY7,,Replicate:
2108,EcBurdQALY8,,Replicate:
2109,EcBurdQALY9,,Replicate:
2110,EcBurdQALY10,,Replicate:
2201,BurdFalsPosQALY1,,Replicate:
2202,BurdFalsPosQALY2,,Replicate:
2203,BurdFalsPosQALY3,,Replicate:
2204,BurdFalsPosQALY4,,Replicate:
2205,BurdFalsPosQALY5,,Replicate:
2206,BurdFalsPosQALY6,,Replicate:

2207,BurdFalsPosQALY7,,Replicate:
2208,BurdFalsPosQALY8,,Replicate:
2209,BurdFalsPosQALY9,,Replicate:
2210,BurdFalsPosQALY10,,Replicate:
2301,BurdFalsPosTreat1,,Replicate:
2302,BurdFalsPosTreat2,,Replicate:
2303,BurdFalsPosTreat3,,Replicate:
2304,BurdFalsPosTreat4,,Replicate:
2305,BurdFalsPosTreat5,,Replicate:
2306,BurdFalsPosTreat6,,Replicate:
2307,BurdFalsPosTreat7,,Replicate:
2308,BurdFalsPosTreat8,,Replicate:
2309,BurdFalsPosTreat9,,Replicate:
2310,BurdFalsPosTreat10,,Replicate;

REPLICATE, 20,,,Yes,Yes,,,,24,Hours;